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## (54) Method and apparatus for treating blood

(57) If pressure constraints occur during the execution of blood treatment, the pump flow rates are rapidly decelerated to remove the pressure constraints so that the treating operation will restore the normal state as quickly as possible. After the pressure constraints have been removed, the pump flow rates are restored at a preset acceleration without causing any excessive pressure buildup due to an abruptly increased load. If the

pump flow rates immediately after the start of operation of the processor are increased through two stages of acceleration, the target flow rates can be rapidly reached without exerting any abrupt load on the processor and, hence, without causing an excessive pressure buildup.

FIG. 2A

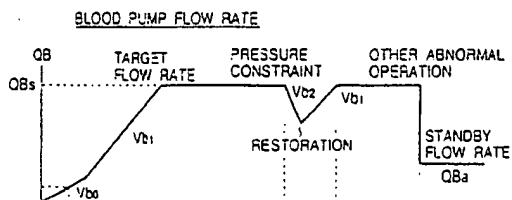
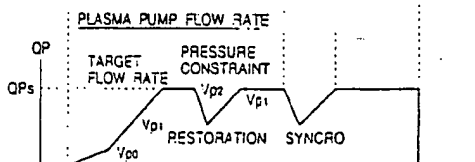


FIG. 2B



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## Description

The present invention relates to a method and an apparatus for treating blood in various ways such as removing impurities and deleterious matter, and replacement of specific components.

5 For the treatment of various diseases, blood is treated in various ways, among which the following are conventionally known: a method in which plasma is separated from a blood sample and loaded on an adsorption column to remove the unwanted or deleterious matter by adsorption; plasma exchange in which the separated plasma is replaced by a replenishing fluid; double filtration for removing higher molecular weight components of the plasma; and artificial dialysis in which the blood sample is brought into contact with a semipermeable membrane.

10 These blood treating methods are implemented with an apparatus of blood treatment which generally comprises a cascade connection of a collection circuit for withdrawing a blood sample by means of a blood pump, a treating circuit for performing specified treatment on the blood sample and a return circuit through which the treated blood sample is returned to the patient. In addition, a heparin pump, a filter, a blood warmer, an air bubble detector, as well as a plurality of pressure gauges and clamp valves are provided at appropriate sites in the respective circuits. If the apparatus is a type that treats a separated plasma component of blood, a plasma separator, a plasma pump, a blood leak detector, an adsorber or a secondary filter and the like are also provided in the treatment circuit.

15 The apparatus of blood treatment having the construction described above is usually provided with control means for controlling the driving of the pumps and the opening/closing of the clamp valves such that the blood treatment can be accomplished by automated operation of the apparatus.

20 If any abnormality occurs to the pressures in the circuits or to devices in the apparatus of blood treatment during its use, the operation of the pumps has to be controlled in an appropriate way depending on the nature of the abnormality. According to Examined Japanese Patent Publication Nos. 28981/1990 and 50304/1993, if the blood withdrawing portion of an apparatus of blood treatment becomes constricted during treatment to produce a great negative pressure in the primary flow channel to the first pump, a further increase in the negative pressure can be avoided by reducing the rotating speeds of the first and second pumps while keeping the ratio between their flow rates constant.

25 This method is capable of dealing with the increase in negative pressure that occurs in the primary flow channel to the first pump on account of the constriction of the blood withdrawing portion of the apparatus of blood treatment. However, neither of the patents mentioned above disclose a technique for controlling the pumps when other abnormal events occur and while the operation restores the normal state.

30 The present invention provides a technique for achieving safe and efficient blood treatment by controlling the operational state of pumps in an appropriate way when starting the execution of blood treatment, when an abnormal event occurs during the execution of the treatment and while the operation restores the normal state.

35 The apparatus of blood treatment to be used in the invention comprises a collection circuit into which a blood sample is withdrawn by means of a blood pump, a treating circuit for performing specified treatment on the withdrawn blood sample and a return circuit through which the treated blood sample is returned to the patient, with pressure gauges being provided at appropriate sites in the collection, treating and return circuits. The apparatus of blood treatment also includes means for controlling the operation of the blood pump. The present invention is characterized by performing the following steps with the thus constructed apparatus of blood treatment.

40 (1) At the start of the treatment, the blood pump starts to operate and continues to run with the blood flow rate being increased at a preset normal acceleration until a specified target blood flow rate is reached; alternatively, the blood pump may be set in such a way that the blood flow rate is increased through at least two stages of acceleration, one being at a preset initial acceleration and the other at the normal acceleration.

45 (2) Once the blood pump flow rate has reached the target blood flow rate, the operation of the pump is controlled so as to maintain said target blood flow rate thereafter.

(3) If the values of pressure as detected by specified pressure gauges or the values calculated on said pressure values deviate from respective limiting values to cause pressure constraints, the blood pump flow rate is reduced at a specified deceleration.

50 (4) If the pressure constraints are removed, the blood pump flow rate is increased at the normal acceleration so that it is reverted toward the target blood flow rate.

The following step may additionally be performed.

55 (5) If any abnormal event other than the pressure constraints occurs during the operation of the blood pump, the blood pump flow rate is reduced at a specified deceleration and thereafter maintained at a standby flow rate not exceeding a preset limiting value.

The present invention can be applied to any blood treating methods including adsorptive removal, plasma exchange, double filtration and artificial dialysis.

Fig. 1 is a diagram showing schematically the configuration of circuits in an apparatus of plasma treatment according to the first embodiment of the invention;

Fig. 2 is a graph showing how various pumps are controlled in the plasma treating method of the invention;

Fig. 3 is a diagram showing schematically the configuration of circuits in an apparatus of plasma treatment according to the second embodiment of the invention;

Fig. 4 is a diagram showing schematically the flow channels formed after switching between the two adsorbers in the apparatus of plasma treatment according to the second embodiment of the invention;

Fig. 5 is a diagram showing schematically the flow channels used to regenerate one of the two adsorbers in the plasma processor according to the second embodiment of the invention;

Fig. 6 is a diagram showing schematically the configuration of circuits in the apparatus of plasma treatment of the invention;

Fig. 7 is a graph showing how various pumps are controlled in the plasma treating method of the invention;

Fig. 8 is a diagram showing schematically the flow channel used to recover the residual plasma from the plasma fractionator in the apparatus of plasma treatment of the invention; and

Fig. 9 is a diagram showing schematically the fluid channel used to backflush the separation membrane in the plasma fractionator in the apparatus of plasma treatment of the invention.

Fig. 10 is a diagram showing schematically the configuration of circuits in the apparatus of blood treatment of the invention; and

Fig. 11 is a graph showing how various pumps are controlled in the blood treating method of the invention.

Embodiments of the present invention will now be described with reference to the case where it is applied to an adsorptive blood treatment in which plasma is separated from a blood sample and freed of cholesterol by means of an adsorber.

Fig. 1 shows an example of the apparatus of blood treatment for use in such adsorptive blood treatment. The apparatus comprises basically a collection circuit for withdrawing a blood sample and supplying it into a plasma separator by means of a blood pump, a treating circuit in which the plasma separated from the blood sample by means of the plasma separator is directed into a plasma pump, where it is freed of the unwanted cholesterol, and a return circuit in which the treated plasma is combined with the blood permeate from the plasma separator and then returned to the patient.

Provided at appropriate sites in the circuits are a pressure gauge P3, drip chambers D1, D2, D4, D6 and D7 fitted with pressure gauges P1, P2, P4, P6 and P7, as well as flow channel controlling clamp valves V6, V7, V9, V12, V13, V14 and V15. Also provided are an infuser of anticoagulant heparin, a blood leak detector for detecting the leakage of blood into the plasma emerging from the plasma separator, a blood warmer for warming the returning blood to a specified temperature, an air bubble detector for detecting the entrance of air bubbles into the returning blood, and any other necessary devices.

The operation of the blood and plasma pumps, as well as the opening/closing of the clamp valves are controlled by control means including a CPU, a blood flow rate setting device and a plasma flow ratio setting device on the basis of such information as detection signals from the associated machine parts and the pressure gauges.

The clamp valves are ON/OFF controlled in operative association with the pumps to switch one flow channel to another in each of the steps involved, such as preparatory steps for setting up the circuits and rinsing their interiors with physiological saline prior to the start of blood treatment, the step of introducing a blood sample into the circuits so that it is subjected to plasma treatment with an adsorber and the step of recovering the residual blood in the circuits after the treatment. The control means controls the opening/closing of the clamp valves such as to form an appropriate flow channel for each of these steps.

The method of treating blood with the above-described apparatus of blood treatment is outlined below. In the following description, the pressures measured with the pressure gauges P1, P2 ... are designated P1, P2 ..., respectively, for the sake of convenience.

The blood treating steps will generally proceed in the following way. Usually, the execution of blood treatment is preceded by the preparatory steps of setting up the respective circuits and rinsing their interior with physiological saline. When the required preparatory steps end, the blood pump is started to run so that a blood sample is withdrawn into the collection circuit through the collection tip and thence supplied into the plasma separator. The plasma separated from the blood in the plasma separator is forced by means of the plasma pump through the (plasma) treating circuit to be directed into the adsorber. As it passes through the adsorber, the plasma makes contact with the adsorbent in the adsorber, whereby the unwanted cholesterol is removed from the plasma. The treated plasma emerging from the adsorber is combined with the blood permeate from the plasma separator and returned to the patient through the return circuit. When the necessary treatment has been performed in this way, physiological saline is introduced into the circuits such that the residual blood and plasma are recovered from the circuits and returned to the patient.

In these blood treating steps, the operation of the blood pump is controlled in such a way that the monitored values of a blood collection pressure P1, a venous blood pressure P7 and a differential pressure across the plasma separator

$\Delta P2/6 (= P2 - P6)$  will not exceed the limits of the respective values. If it is found that none of the monitored values have caused pressure constraints after the start of pump operation, the blood pump flow rate QB is increased at a preset initial acceleration  $Vb_0$  until the integrated blood flow reaches a specified value, which is typically set to be approximately equal to the sum of the capacities of the collection circuit and the plasma separator.

5 When the integrated blood flow has reached the specified value, the initial acceleration  $Vb_0$  of the blood pump flow rate is changed to the normal acceleration  $Vb_1$  and the pump operation is continued until the desired target blood flow rate Qbs is reached. After Qbs is reached, the operation of the blood pump is controlled such as to maintain said target blood flow rate.

In order to ensure that an abrupt load is not exerted on a treating device such as the plasma separator to cause an excessive pressure buildup, the initial acceleration  $Vb_0$  is usually set at a lower value than the normal acceleration  $Vb_1$ . However, this is not always the case and depending on the specific situation of the treatment,  $Vb_0$  may be set to be greater than  $Vb_1$ .

If the pressure values of P1, P2 and  $\Delta P2/6$  being monitored with the associated pressure gauges deviate from the respective limiting values to cause pressure constraints, the blood pump flow rate is reduced at a specified deceleration  $Vb_2$ , which is set at a sufficiently great value to ensure that the pressure constraints can be removed rapidly. If the pressure constraints are removed, the blood pump flow rate is increased at the normal acceleration  $Vb_1$  until the target blood flow rate Qbs is restored.

Thus, in the present invention, if pressure constraints are exerted, the blood pump flow rate is reduced at a comparatively large deceleration, thereby allowing for rapid restoration of the machine operation from the abnormal pressure state. During the restoration, the blood flow rate is increased mildly enough to avoid the excessive pressure buildup due to an abruptly increasing load and this enables the blood pump to be operated for a prolonged period without undergoing any constraints.

Even if the blood pump is controlled to maintain the target blood flow rate Qbs, abnormal events other than the above-described pressure constraints may occur, as exemplified by abnormal pressure values detected by pressure gauges other than P1, P2 and P6, or the abnormal operation of certain valves. In this case, the blood pump flow rate may be decelerated momentarily at a sufficiently great deceleration  $Vb_3$  to cause a drop to a standby flow rate QBa, which is maintained until the machine operation restores from the abnormal state. The standby flow rate QBa is set at a value that is lower than a preset upper limit but not so low as to cause blood coagulation in the circuits.

The above-described procedure of controlling the blood pump flow is illustrated by a timing chart in Fig. 2, which also shows the procedure of controlling the plasma pump flow.

Referring now to the plasma pump, it remains at rest as long as the blood pump flow rate QB is below a prescribed value after the blood pump started to run. If the plasma pump is actuated simultaneously with the blood pump, the force to extract plasma will develop before the blood sample is fed into the plasma separator and an extra load is imposed on machine parts. In order to prevent this difficulty, a certain time lag is provided before the plasma pump is actuated.

35 When the blood pump flow rate QB has reached the prescribed value, the plasma pump is started to run and controlled in such a way that the monitored values of  $TMP [(P2 + P6)/2 - P3]$  which represents the pressure difference across the separation membrane in the plasma separator and  $\Delta P4/6 (= P4 - P6)$  representing the pressure difference across the adsorber will not exceed the respective limiting values. If no such pressure constraints are experienced by the plasma pump after the start of its operation, the plasma pump flow rate QP is increased at a preset initial acceleration  $Vp_0$  until the integrated flow reaches a specified value. When the integrated flow has reached the specified value, the initial acceleration  $Vp_0$  is switched to a normal acceleration  $Vp_1$  and the plasma pump flow rate QP is increased until it reaches the target plasma flow rate QPs.

The target plasma flow rate QPs is given as a function of QB (= the blood pump flow rate) and TMP (= the pressure difference across the separation membrane in the plasma separator). In other words, the plasma pump is controlled to attain the target plasma flow rate QPs which is calculated at every moment on the basis of both the ratio determined from TMP and the actual value of blood pump flow rate QB. The value of integrated plasma flow at which the initial acceleration  $Vp_0$  is switched to the normal acceleration  $Vp_1$  is determined on the basis of the capacity of the secondary side (plasma volume) of the plasma separator.

In order to ensure that an abrupt load is not exerted on the separation membrane in the plasma separator to cause an excessive pressure buildup, the initial acceleration  $Vp_0$  is usually set at a lower value than the normal acceleration  $Vp_1$ . However, this is not always the case and depending on the specific situation of the processing,  $Vp_0$  may be set to be greater than  $Vp_1$ .

If the values of pressures TMP and  $\Delta P4/6$  being monitored with the associated pressure gauges deviate from the respective limiting values to cause pressure constraints, the plasma pump flow rate QP is reduced at a specified deceleration  $Vp_2$ , which is set at a sufficiently great value to ensure that the pressure constraints can be removed rapidly. If the pressure constraints are removed, the plasma pump flow rate QP is increased at the normal acceleration  $Vp_1$  such that it is reverted to the target plasma flow QPs.

Thus, in the present invention, if pressure constraints are exerted, pump flows are reduced at comparatively large

decelerations, thereby allowing for rapid restoration of the machine operation from the abnormal pressure states. During the restoration phase, the pump flows are increased mildly enough to avoid the excessive pressure buildup due to an abruptly increasing load and this enables the pumps to be operated for a prolonged period without undergoing any constraints.

5 If the blood pump flow is to be reduced due to pressure constraints while the plasma pump is running normally, the plasma pump flow rate QP is reduced synchronously. In this case, the plasma pump flow rate QP is determined on the basis of blood pump flow rate QB by the same technique as employed to calculate the target plasma flow rate QPs. It should, however, be noted that if the blood pump flow rate QB becomes lower than the prescribed value, the plasma pump is brought to a stop.

10 The above-described procedures of controlling the pump flows are illustrated by timing charts in Fig. 2.

The foregoing discussion is directed to the case of applying the present invention to the processing a blood sample such that the unwanted matter is removed from plasma by means of an adsorber. This is not the sole applicable case of the invention and it may be applied to other blood treating methods including the double filtration of plasma, plasma exchange and artificial dialysis. If the invention is to be applied to these cases, the procedure of controlling the blood pump operation suffices to be modified in accordance with the specific embodiment of a respective blood treating method.

An example of the method of setting conditions for the case of executing the plasma treating steps by means of the apparatus of plasma treatment shown in Fig. 1 will now be described below.

20 Immediately after the start of operation of the blood pump, the blood flow rate QB is increased at the initial acceleration  $Vp_0$  which is set at an appropriate value within the range of 20 to 100 mL/min/min. When the integrated blood flow has reached 300 mL which is approximately equal to the sum of the capacities of the collection circuit and the plasma separator, the initial acceleration  $Vp_0$  is switched to the normal acceleration  $Vp_1$  which is set at an appropriate value within the range of 20 to 150 mL/min/min and the blood pump flow rate is increased until the target blood flow rate QBs (= 100 mL/min) is reached. The initial acceleration  $Vb$  is typically set to be smaller than the normal acceleration  $Vp_1$  but this is not always the case of the invention. When the blood flow rate has reached the target value QBs, the operation of the blood pump is controlled so as to maintain QBs.

The operation of the blood pump is controlled in such a way that the monitored values of the blood collection pressure P1, the venous blood pressure P7 and the pressure difference across the plasma separator  $\Delta P2/6$  will not exceed the limits of the respective values. If either one of said pressures deviates from the associated limiting value to cause a pressure constraint, namely, if P1 becomes lower than the lower limit, or if P7 exceeds the upper limit, or if  $\Delta P2/6$  becomes greater than the upper limit, the blood pump flow rate QB is rapidly reduced at a sufficiently great deceleration of  $Vp_2$  (= 300 mL/min/min) to ensure that the pressure constraint is removed as soon as possible. When the pressure constraint is removed, the blood pump flow rate QB is increased again at the normal acceleration  $Vp_1$  such that it is reverted toward the target blood flow rate QBs (= 100 mL/min).

35 If there occurs any abnormal event other than the pressure constraints, as exemplified by abnormal operation of valves, and yet the blood pump is running without trouble, the blood pump flow rate QB is rapidly decelerated to the standby flow rate QBa ( $\leq 50$  mL/min) which is preset by a blood flow rate setting device and the blood circulation is continued by controlling the blood pump such as to maintain QBa. If the abnormal event under consideration is removed, QB is reverted toward the target value QBs. The procedure of executing the restoration of QBs has already been described above.

40 Referring now to the plasma pump, it remains at rest until after the blood pump has run to attain a QB value of 15 mL/min. When QB has reached 15 mL/min, the plasma pump is started to run with TMP (=  $(P2 + P6)/2 - P3$  the pressure difference across the separation membrane in the plasma separator) and  $\Delta P4/6$  (=  $P4 - P6$  = the pressure difference across the adsorber) being monitored. Until after the integrated plasma flow has reached 50 mL which is approximately equal to the volume of plasma on the secondary side of the plasma separator, the plasma pump flow rate QP is increased at an initial acceleration of  $Vp_0$  which is set within the range of 10 to 60 mL/min/min. Once the integrated plasma flow has reached 50 mL, the plasma pump flow rate QP is increased at a normal acceleration  $Vp_1$  (10 to 100 mL/min/min) until it reaches the target plasma flow rate QPs. In order to ensure that the load on the machine parts will increase mildly, the normal acceleration  $Vp_1$  is usually set to be greater than the initial acceleration  $Vp_0$ .

50 The plasma pump is controlled at every moment such as to maintain the target plasma flow rate QPs which is calculated on the basis of QB and TMP.

The target plasma flow rate QPs is expressed as  $QPs = K \cdot R1 \cdot QB$ , where QB is the blood pump flow rate. K is a coefficient of plasma flow ratio which is preset by a plasma flow ratio setting device and R1 is a coefficient defined below on the basis of TMP:

55

$$R1 = 1.0 - (TMP/\text{upper limit of TMP}) \cdot (1.0 - r)$$

where r is a coefficient of the upper limit of pressure difference and set at an appropriate value between 0.0 (inclusive)

and 1.00 depending on the degree of internal plugging of the separation membrane. Depending on the properties of the blood to be processed and the quality of the separation membrane, the separation membrane occasionally has a great tendency to be plugged. If it is empirically known that the separation membrane is likely to be plugged, the value of  $r$  is set in the lower range. On the other hand, if it is empirically known that the separation membrane is free from the potential plugging, the value of  $r$  may be set in the higher range.

The coefficient of plasma flow ratio  $K$  is a parameter which is set by the plasma flow ratio setting device in consideration of the performance of the plasma separator and the properties of the blood to be processed and it is generally set within the range of 0.2 to 0.4, typically within the range of 0.25 to 0.35.

The operation of the plasma pump is controlled on the basis of the monitored values of TMP which represents the pressure difference across the separation membrane in the plasma separator and  $\Delta P4/6 (= P4 - P6)$  representing the pressure difference across the adsorber. If TMP or  $\Delta P4/6 (= P4 - P6)$  deviates from the respective limiting value, the plasma pump flow rate QP is rapidly reduced at the specified deceleration  $Vp_2$  (e.g., 140 mL/min/min). If the pressure constraint is eventually removed, QP is increased again at the normal acceleration  $Vp_1$  so that it is reverted toward the target plasma flow rate QPs.

It should be noted that the limiting values of the various pressures to be monitored, namely, the lower limit of blood correction pressure  $P1$ , the upper limit of venous blood pressure  $P7$ , the upper limit of the pressure difference across the plasma separator  $\Delta P2/6$ , the upper limit of the pressure difference across the separation membrane TMP and the upper limit of the pressure difference across the adsorber  $\Delta P4/6$ , are each set to be a little lower than the threshold for the issuance of an alarm signal so as to assure safety in the treating operations. Specifically, a difference of about 20 mmHg is provided between the threshold and the respective limiting value.

The plasma pump is not operated independently of the blood pump but the two pumps are controlled in operative association with each other. Even if the plasma pump is running normally, it may become necessary to reduce the blood pump flow rate QB on account of a pressure constraint; in that case, the plasma pump flow rate QP is reduced synchronously such that the relation  $QP = K \cdot R1 \cdot QB$  (for the definitions of  $K$  and  $R1$ , see above) is maintained at all times. If the blood pump flow rate QB is adjusted to be equal to the standby flow rate QBa when an abnormal event (as in valves) which is other than pressure constraints occurs, the plasma pump is brought to a stop.

In the embodiment under consideration, the plasma pump is so set that it will stop running if the blood pump flow rate QB falls below a certain value (e.g. 15 mL/min). It should, however, be noted that the lower limit of QB below which the plasma pump is brought to a stop is not necessarily 15 mL/min but may be determined as appropriate for parameters such as the performance of the pumps.

After the pressure constraints and other abnormal events are removed, the plasma pump flow rate QP is restored from the rest state and the procedure for the restoration is essentially the same as the already-described procedure for starting the operation of the plasma pump.

The second embodiment of the invention is shown in Fig. 3 and relates to an apparatus for removing the unwanted cholesterol from plasma in two adsorbers. In this particular embodiment, two adsorbers A and B are provided in parallel in the plasma circuit and flow channels are formed in such a way that the two adsorbers can be operated alternately; in addition, while one adsorber is being used, the other is reactivated with a regenerating fluid, thereby enabling both adsorbers to be used repeatedly such that plasma is processed with the regeneratable adsorbers.

The apparatus of plasma treatment used in the second embodiment shares the blood collection and return circuits with the apparatus of plasma treatment of the first embodiment. However, the plasma circuit differs in that two branches are formed downstream of the plasma pump and respectively provided with two parallel adsorbers A and B of the same capacity; in addition, a replacement fluid pump is provided upstream of the adsorbers A and B and connected to means for supplying a regenerating fluid (a concentrated aqueous solution of an electrolyte such as sodium chloride) and means for supplying a replacement fluid (e.g. physiological saline or Ringer's solution). Switching between the parallel adsorbers A and B, as well as the feeding of each adsorber with a suitable fluid selected from among plasma, regenerating fluid and replacement fluid can be accomplished by opening or closing valves  $V1$  to  $V11$ . Another feature to be added in the second embodiment is a drip chamber D5 fitted with a pressure gauge P5 for detecting the pressure between the replacement fluid pump and either adsorber.

Using the thus constructed apparatus of plasma treatment of a regeneratable type, plasma will be treated in accordance with the following procedure. After the specified preparatory steps such as setting up the respective circuits and rinsing their interior have ended, a blood sample is withdrawn into the collection circuit by means of the blood pump and plasma is separated from the blood in the plasma separator. The separated plasma is directed into one of the two adsorbers by means of the plasma pump. The method of controlling the pumps in such plasma treating steps is substantially the same as in the first embodiment. Stated specifically, after the blood pump is turned on, the blood pump flow rate is first increased at the initial acceleration  $Vb_0$  which is set at an appropriate value in the range of 20 to 100 mL/min/min; when the integrated blood flow has reached 300 mL, the initial acceleration  $Vb_0$  is switched to the normal acceleration  $Vb_1$  which is set at an appropriate value in the range of 20 to 150 mL/min/min and the blood pump flow rate is increased until the target value QBs ( $= 100$  mL/min) is reached. When QBs has been reached, the blood pump is con-

trolled such as to maintain this value based on the monitored values of P1, P2 and  $\Delta P2/6$ .

Referring now to the plasma pump, it remains at rest until after the blood pump has run until the blood pump flow rate QB reaches 15 mL/min. When QB has reached 15 mL/min, the plasma pump is started to run. In this case, the associated valves are manipulated to form a flow channel that permits the plasma to flow only into the adsorber A. The plasma pump flow rate QP is increased at the initial acceleration  $Vp_0$  (10 - 60 mL/min/min) until the integrated plasma flow reaches 50 mL. After the integrated plasma flow has reached 50 mL, QP is increased at the normal acceleration  $Vp_1$  which is set at an appropriate value in the range of 10 to 100 mL/min/min until the target plasma flow rate QPs is reached. The target value QPs is the product of multiplication of QBs (= the target blood flow rate for the blood pump) by K (= the coefficient of plasma flow ratio which is preset by the plasma flow ratio setting device) and R1 which is determined from TMP (= the pressure difference across the separation membrane in the plasma separator). When QPs has been reached, the plasma pump is controlled at every moment such as to maintain this value based on the monitored values of TMP and  $\Delta P4/6$ .

If the blood pump undergoes a pressure constraint in association with either one of P1, P7 and  $\Delta P2/6$ , the blood pump flow rate QB is reduced rapidly at the deceleration  $Vb_2$  (= 300 mL/min/min) to ensure that the pressure constraint is removed as soon as possible. When the pressure constraint is removed, the blood pump flow rate QB is increased at the normal acceleration  $Vb_1$  such that it is reverted toward the target blood flow rate QBs (= 100 mL/min).

As in the case of the blood pump, if the plasma pump undergoes a pressure constraint in association with TMP or  $\Delta P4/6$ , the plasma pump flow rate QP is reduced rapidly at the specified deceleration  $Vp_2$  (e.g. 140 mL/min/min). If the pressure constraint is removed, the plasma pump flow rate QP is increased again at the normal acceleration  $Vp_1$  such that it is reverted toward the target plasma flow rate QPs.

If an abnormal event (as in valves) which is other than the pressure constraints occurs, the blood pump is decelerated rapidly only when it is running without any troubles and blood circulation is effected by controlling the blood pump provide the standby flow rate QBa which is set by the blood flow rate setting device so as not to exceed 50 mL/min. In this case, the plasma pump should in principle be brought to a stop. When the abnormal event under consideration is removed, the blood pump flow rate QB is reverted toward the target value QBs.

If a pressure constraint develops to cause the necessity of reducing the blood pump flow rate QB, the plasma pump flow rate QP is reduced synchronously. In this case, too, the plasma pump flow rate QP is controlled to maintain the relation  $QP = K \cdot R1 \cdot QB$ . In addition, the plasma pump is so set that if the blood pump flow rate QB has fallen below 15 mL/min, it stops running.

If, as the result of execution of plasma treatment, the treating capacity of adsorber A has dropped below a certain level or if the integrated throughput has reached a specified value, the present set of flow channels is switched to another set of flow channels by manipulation of the associated clamp valves; in the new set of flow channels, the replacement fluid (e.g., physiological saline) is flowed into the adsorber A by means of the replacement fluid pump and the plasma is flowed into the adsorber B, with the outlet portion of the adsorber A being connected to the return circuit whereas the outlet portion of the adsorber B is connected to the reject flow channel. The configuration of the flow channels just described above is shown in Fig. 4.

Subsequently, the adsorber A is supplied with the replacement fluid by means of the replacement fluid pump and the plasma is forced out of the adsorber A to be returned to the patient through the return circuit. On the other hand, the adsorber B is supplied with an incoming flow of plasma, which displaces the internal preservative fluid such that the latter is discharged through the reject flow channel. When the plasma has been forced out of the adsorber A such that its interior is filled up by the replacement fluid, the outlet portion of the adsorber A is disconnected from the return circuit and connected to the reject flow channel. Similarly, when the interior of the adsorber B has become devoid of the permeate to be filled up with the plasma, the outlet portion of the adsorber B is disconnected from the reject flow channel and connected to the return circuit so that the plasma treatment is continued by operation of the adsorber B.

While the plasma is being treated with the adsorber B, a flow channel is formed to establish communication between the inlet portion of the adsorber A and the regenerating fluid supply means such that the regenerating fluid is fed into the adsorber A by means of the replacement fluid pump. The regenerating fluid regenerates the adsorbent in the adsorber A so that its adsorptive power is restored. The configuration of flow channels formed in this case is shown in Fig. 5.

When the passage of the regenerating fluid has reached a specified value, the inlet portion of the adsorber A is allowed to communicate again with the replacement fluid supply means and the replacement fluid is supplied so that the regenerating fluid is discharged from within the adsorber A. Since the regenerating fluid has a higher salt concentration than the physiological level, it need be replaced by the replacement fluid to ensure that the interior of the adsorber A is restored to the physiological concentration.

The reject flow channel is provided with a salinometer by means of which one can confirm that the regenerating fluid has been completely replaced by the replacement fluid to provide a reject in which the salt concentration has been reverted to the physiological level.

Thus, the adsorptive capacity of the adsorber A has been restored and its interior has been filled up with the

replacement fluid. When the adsorptive capacity of the other adsorber B has thereafter fallen below a certain level or if the integral throughout has reached a specified value, the same procedure as described above may be employed to switch from adsorber B to A for performing plasma treatment. The adsorber B is then subjected to the same regeneration process as applied to the adsorber A, thereby recovering the adsorptive capacity of B. In this way, the two adsorbers A and B can be used alternately after the necessary regeneration process is performed and, hence, a large volume of plasma can be treated continuously even if these adsorbers have a comparatively small capacity.

The replacement fluid pump is operated by a method which is substantially the same as the method of operating the plasma pump. Specifically, immediately after the start of its operation, the replacement fluid pump flow rate QR is increased at an initial acceleration  $Vr_0$  which is set within the range of 10 to 60 mL/min/min. When the integrated flow has reached 50 mL, QR is increased at a normal acceleration  $Vr_1$  which is set at an appropriate value within the range of 10 to 100 mL/min/min until the target replacement fluid flow rate QRs is reached. The target replacement fluid flow rate QRs is the product of multiplication of QBs (= the target blood flow rate for the blood pump) and the coefficient R1 which is determined from TMP (= the pressure difference across the separation membrane in the plasma separator). In other words, QRs representing the target replacement fluid flow rate for the replacement fluid pump is set to be substantially equal to QPs which represents the target plasma flow rate for the plasma pump. If this condition is met, switching between the two adsorbers can be accomplished without compromising the purpose of realizing smooth continuation of the plasma treatment because the speed at which the replacement fluid forces the plasma out of the adsorber A is equal to the speed at which plasma flows into the other adsorber B.

After the target replacement fluid flow rate QRs has been reached, the replacement fluid pump is controlled so as to maintain that value based on the monitored value of  $\Delta P5/6$  (=  $P5 - P6$ ) which represents the pressure difference across each adsorber.

If the pressure being monitored deviates from the limiting value to cause a pressure constraint, the replacement fluid pump flow rate QR is rapidly reduced at a specified deceleration  $Vr_2$  (e.g. 140 mL/min/min). If the pressure constraint is eventually removed, QR is increased again at the normal acceleration  $Vr_1$  so that it is reverted toward the target replacement fluid flow rate QRs.

Even if the replacement fluid pump is running normally, it may become necessary to reduce the blood pump flow rate QB on account of a certain abnormality such as a pressure constraint; in that case, the replacement fluid pump flow rate QR is reduced synchronously at the deceleration which is controlled to be equal to QB multiplied by K and R1 (for their definitions, see above). In the second embodiment of the invention, the replacement fluid pump is so set that it will stop running if the blood pump flow rate QB falls below 15 mL/min. If the pressure constraint and other abnormal events have been removed, the replacement fluid pump flow rate QR is restored by a procedure which is substantially the same as described above.

According to the forgoing embodiments of the present invention, plasma is treated in such a way that when the pressures being monitored by specified pressure gauges deviate from the respective limiting values to cause pressure constraints, various pump flow rates are reduced rapidly enough to ensure that the pressure constraints can be removed as soon as possible. After the pressure constraints are removed, the pump flow rates are restored at preset accelerations, again ensuring that there will be no excessive pressure buildups due to abruptly increasing loads.

If the blood pump flow rate is increased through two stages of acceleration when a blood sample is introduced immediately after the apparatus is started to operate, there will be no possibility of imposing an abrupt load on the apparatus and the target blood flow rate can be rapidly reached without causing a pressure buildup exceeding the limiting value. This is also true with the plasma pump and if its flow rate is increased through two stages of acceleration, the desired target plasma flow rate can be rapidly reached without causing a departure from the limiting value of pressure.

If any abnormal event other than pressure constraints occurs while the blood pump is operating normally, the blood pump is controlled in such a way that its flow rate is decelerated rapidly while a standby flow rate is maintained at a value not exceeding a preset upper limit; this ensures safety in the blood treatment without stopping its flow, thereby preventing the blood from being coagulated in the circuits.

If the plasma pump flow rate is controlled as a function of the pressure difference across the separation membrane in the plasma separator, it can be set at an optimal value reflecting the degree of plugging of the separation membrane which is variable at every moment. As a result, the progress of the plugging of the separation membrane can be retarded and the required plasma treatment can be accomplished without being interrupted or undergoing some constraints.

Fig. 6 shows an apparatus for treating plasma by double filtration and comprises basically a collection circuit for withdrawing a blood sample and feeding it into a plasma separator by means of a blood pump, a plasma circuit in which the plasma separated in the plasma separator is directed by means of a plasma pump into a plasma fractionator, where it is fractionated into a high-molecular weight component and a low-molecular weight component, the latter being returned to the patient, an ejection channel through which the high-molecular weight component of the plasma is discharged by means of a replacement fluid pump, a replenishing fluid supply channel which communicates replenishing solution supply means with the plasma circuit via the replacement fluid pump, and a return circuit in which the low-

molecular weight component of the plasma as supplied with the replenishing fluid is combined with the blood permeate from the plasma separator and the replenishing fluid and returned to the patient.

In the embodiment to be described below, a replacement fluid pump of a twin type is employed. This provides for simultaneous fitting of two tubes, one serving as a channel for discharging the high-molecular weight component of plasma and the other serving as a flow channel for feeding the replenishing fluid. As a result, the discharge of the high-molecular weight component of plasma through the first tube and the passage of the replenishing fluid through the second tube can be accomplished simultaneously with a single pump unit, thereby assuring the high-molecular weight component of plasma to be exchanged with an equal volume of the replenishing fluid.

Provided at appropriate sites in the circuits are pressure gauges P3 and P5, drip chambers D1, D2, D4, D6 and D7 fitted with pressure gauges P1, P2, P4, P6 and P7, as well as valves V1 to V10 and V12 to V15 for performing ON/OFF and switching control over the flow channels. Also provided are infusers of physiological saline for rinsing the circuits and recovering the residual blood, an infuser of anticoagulant heparin, a blood leak detector for detecting the leakage of blood into the plasma emerging from the plasma separator, a blood warmer for warming the returning blood to a specified temperature, an air bubble detector for detecting the entrance of air bubbles into the returning blood, fluid shortage detectors for checking the supply of physiological saline and the replenishing fluid, and any other necessary devices.

The procedure of plasma treatment by double filtration will now be outlined. Usually, the execution of plasma treatment is preceded by the preparative steps of setting up the respective circuits and rinsing their interior with physiological saline. When the required preparative steps end, the blood pump is started to run so that a blood sample is withdrawn into the collection circuit through the collection tip and thence supplied into the plasma separator. The plasma separated from the blood in the plasma separator is forced by means of the plasma pump to be directed into the plasma fractionator, where it is fractionated into the high-molecular weight component and the low-molecular weight component. The high-molecular weight component of plasma contains deleterious or unwanted matter and, hence, is discharged through the ejection channel by means of the replacement fluid pump. As already mentioned, the replacement fluid pump is of a twin type which is fitted with both the tube serving as a channel for discharging the high-molecular weight component of plasma and the tube serving as a channel for feeding the replenishing fluid; hence, as the high-molecular weight component of plasma is discharged, the same volume of the replenishing fluid is supplied from its supply means into the low-molecular weight component of plasma through the associated feed channel. The thus replenished low-molecular weight component of plasma is combined with the blood permeate from the plasma separator and returned to the patient through the blood warmer. When a specified amount of plasma has been treated, physiological saline is introduced into the circuits such that the residual plasma and blood are recovered from the circuits and returned to the patient.

The replacement fluid pump is adapted to be such that if the monitored value of  $TMP2 (= P4 - P5)$  which represents the pressure difference across the separation membrane in the plasma fractionator is less than a preset threshold pressure  $P\alpha$  ( $TMP2 < P\alpha$ ), it will not start to run whereas if  $TMP2$  is equal to or greater than  $P\alpha$  ( $TMP2 \geq P\alpha$ ), it will start to run. This is because if the replacement fluid pump is actuated before  $TMP2$  has rose sufficiently to reach  $P\alpha$ , the low-molecular weight component of plasma can potentially be lost into the high-molecular weight component being discharged.

On the other hand, if  $TMP2$  is equal to or greater than  $P\alpha$ , it can safely be concluded that the high-molecular weight component of plasma is being effectively separated from the low-molecular weight component in the plasma fractionator. Therefore, if the replacement fluid pump is adapted to run only if  $TMP2 \geq P\alpha$ , there is no possibility for the low-molecular weight component of plasma to be lost into the high-molecular weight being discharged. In addition, if  $TMP2$  becomes less than the pressure setting  $P\alpha$  during the operation of the replacement fluid pump because of abnormality in a certain device such as the plasma fractionator, the plasma circuit or valves, the replacement fluid pump is immediately brought to a stop so as to prevent the loss of plasma.

After the start of operation of the replacement fluid pump, its flow rate  $QR$  is increased at a specified acceleration  $Vr_1$  toward the target replacement fluid flow rate  $QRs$  which is preset by a replacement fluid flow rate setting device. It should, however, be noted that  $QR$  satisfies the condition that it be by no means greater than a prescribed flow rate  $QRa = cQP$  ( $0 < c < 1$ ). In other words,  $QR$  or the replacement fluid pump flow rate is controlled to be such that it is always equal to whichever smaller of the target replacement fluid flow rate  $QRs$  or the prescribed flow rate  $QRa$ . By this control, the rate of discharging the high-molecular weight component of plasma is effectively restricted to prevent the loss of the low-molecular weight component of plasma into the high-molecular weight.

While the replacement fluid pump is operated to provide the target replacement fluid flow rate  $QRs$ , abnormal events such as pressure constraints may give rise to the need for reducing the plasma pump flow rate  $QP$ , with the result the prescribed flow rate  $QRa$  which depends on  $QP$  becomes lower than the target replacement fluid flow rate  $QRs$ . In this case, the replacement fluid pump flow rate  $QR$  is reduced to the prescribed flow rate  $QRa$ .

When the abnormal event such as pressure constraints are removed and the plasma pump flow rate  $QP$  is restored, eventually causing the prescribed flow rate  $QRa$  to exceed the target replacement fluid flow rate  $QRs$ , the

replacement fluid pump flow rate is increased again toward QRs at an acceleration which is set at  $Vr_1$ .

Generally speaking, if the settings of pump flow rates are very small, the operation of the pumps becomes unstable, causing frequent fluctuations in their flow rates. Therefore, if the target replacement fluid flow rate QRs for the replacement fluid pump is set below a certain value or if the prescribed flow rate QRa becomes lower than a certain value due to the drop in the plasma pump flow rate, the replacement fluid pump is controlled to perform an intermittent operation, in which it runs and stops alternately. By executing such intermittent operation, one can assure the precision in the rotation of the replacement fluid pump in an extremely small flow rate range, thereby permitting the replacement fluid flow rate to be stabilized. In addition, the intermittent operation of the replacement fluid pump is equivalent to the case of opening and closing the ejection channel continually, thereby making it possible to ensure that TMP2 which represents the pressure difference across the separation membrane in the plasma fractionator is maintained at a high level. As a result, the efficiency of separation of the low-molecular weight component of plasma from the high-molecular weight component is sufficiently improved to prevent the loss of plasma. The value of QRs or QRa at which the replacement fluid pump is allowed to operate intermittently is determined as appropriate for the performance of the pump.

The above-described procedures for the control of the blood pump, plasma pump and the replacement fluid pump may be represented graphically in Fig. 7.

#### (Plasma treating steps)

An example of the method of setting conditions for the case of executing the plasma treating steps by means of the apparatus of plasma treatment shown in Fig. 6 will now be described below.

Immediately after the start of operation of the blood pump, its flow rate QB is increased at the initial acceleration  $Vb_0$  which is set at an appropriate value within the range of 20 to 100 mL/min/min. When the integrated blood flow has reached 300 mL which is approximately equal to the sum of the capacities of the collection circuit and the plasma separator, the initial acceleration  $Vb_0$  is switched to the normal acceleration  $Vb_1$  which is set at an appropriate value within the range of 20 to 150 mL/min/min and the blood pump flow rate is increased until the target flow rate QBs (= 100 mL/min) is reached. The initial acceleration  $Vb_0$  is typically set to be smaller than the normal acceleration  $Vb_1$ , but this is not always the case of the invention. When the blood flow rate has reached the target blood flow rate QBs, the operation of the blood pump is controlled so as to maintain QBs.

The operation of the blood pump is controlled in such a way that the monitored values of the blood collection pressure P1, the venous blood pressure P7 and the pressure difference across the plasma separator  $\Delta P2/P6$  will not exceed the limits of the respective values. If either one of said pressures deviates from the associated limiting value to cause a pressure constraint, namely, if P1 becomes lower than the lower limit, or if P7 exceeds the upper limit, or if  $\Delta P2/P6$  becomes greater than the upper limit, the blood pump flow rate QB is rapidly reduced at a sufficiently great deceleration of  $Vb_2$  (= 300 mL/min/min) to ensure that the pressure constraint is removed as soon as possible. When the pressure constraint is removed, the blood pump flow rate QB is increased again at the normal acceleration  $Vb_1$  until the target blood flow rate QBs (= 100 mL/min) is restored.

If there occurs an abnormal event other than the pressure constraints, as exemplified by abnormal operation of valves, and yet the blood pump is running without trouble, the blood pump flow rate QB is rapidly decelerated to the standby flow rate QBa ( $\leq 50$  mL/min) which is preset by the blood flow rate setting device and the blood circulation is continued by controlling the blood pump such as to maintain QBa. If the abnormal event under consideration is removed, QB is restored to the target blood flow rate QBs. The procedure of executing the restoration to QBs has already been described above.

Referring now to the plasma pump, it remains at rest until after the blood pump has run to attain a QB value of 15 mL/min. When QB has reached 15 mL/min, the plasma pump is started to run. Until after the integrated plasma flow has reached 50 mL which is approximately equal to the volume of plasma on the secondary side of the plasma separator, the plasma pump flow rate QP is increased at the initial acceleration  $Vp_0$  which is set within the range of 10 to 60 mL/min/min. Once the integrated plasma flow has reached 50 mL, the plasma pump flow rate QP is increased at the normal acceleration  $Vp_1$  (10 to 100 mL/min/min) until it reaches the target plasma flow rate QPs. In order to ensure that the load on the machine parts will increase mildly, the normal acceleration  $Vp_1$  is usually set to be greater than the initial acceleration  $Vp_0$ .

The plasma pump flow rate QP is controlled at every moment such as to maintain the target plasma flow rate QPs which is calculated on the basis of the blood pump flow rate QB and the pressure difference across the separation membrane in the plasma separator which is denoted by TMP1 [ $= (P2 + P6)/2 - P3$ ].

The target plasma flow rate QPs is expressed as  $QPs = K \cdot R1 \cdot QB$ , where QB is the blood pump flow rate, K is a coefficient of plasma flow ratio which is preset by a plasma flow ratio setting device and R1 is a coefficient defined below on the basis of TMP1:

$$R1 = 1.0 \cdot (TMP1/\text{upper limit of TMP1}) \cdot (1.0 - r)$$

where  $r$  is a coefficient of the upper limit of pressure difference and set at an appropriate value between 0.0 (inclusive) and 1.00 depending upon the degree of internal plugging of the separation membrane. Depending upon the properties of the blood to be treated and the quality of the separation membrane, the separation membrane occasionally has a great tendency to be plugged. If it is empirically known that the separation membrane is likely to be plugged, the value of  $r$  is set in the lower range. On the other hand, if it is empirically known that the separation membrane is free from the potential plugging, the value of  $r$  may be set in the higher range.

The coefficient of plasma flow ratio  $K$  is a parameter which is set by the plasma flow ratio setting device in consideration of the performance of the plasma separator and the properties of the blood to be treated and it is generally set within the range of 0.2 to 0.4, typically within the range of 0.25 to 0.35.

If TMP1 deviates from the limiting value, the plasma pump flow rate  $Q_P$  is rapidly reduced at the specified deceleration  $V_{p2}$  (e.g., 140 mL/min/min). If the pressure constraint is eventually removed,  $Q_P$  is increased again at the normal acceleration  $V_{p1}$  so that it is reverted toward the target plasma flow rate  $Q_{Ps}$ .

It should be noted that the limiting values of the various pressures to be monitored, namely, the lower limit of blood collection pressure  $P_1$ , the upper limit of venous blood pressure  $P_7$ , the upper limit of the pressure difference across the plasma separator  $\Delta P_{2/5}$  and the upper limit of the pressure difference across the separation membrane TMP1, are each set to be a little smaller than the threshold for the issuance of an alarm signal so as to assure safety in the processing operations. Specifically, the difference of about 20 mmHg is provided between the threshold and the respective limiting value.

The plasma pump is not operated independently of the blood pump but the two pumps are controlled in operative association with each other. Even if the plasma pump is running normally, it may become necessary to reduce the blood pump flow rate  $Q_B$  on account of a pressure constraint; in that case, the plasma pump flow rate  $Q_P$  is reduced synchronously such that the relation  $Q_P = K \cdot R_1 \cdot Q_B$  (for the definitions of  $K$  and  $R_1$ , see above) is maintained at all times. If the blood pump flow rate  $Q_B$  is adjusted to be equal to the standby flow rate  $Q_{Ba}$  when an abnormal event (as in valves) which is other than pressure constraints occurs, the plasma pump should in principle be brought to a stop.

In the embodiment under consideration, the plasma pump is so set that it will stop running if the blood pump flow rate  $Q_B$  falls below a certain value (e.g. 15 mL/min). It should, however, be noted that the lower limit of  $Q_B$  below which the plasma pump is brought to a stop is not necessarily 15 mL/min but may be determined as appropriate for parameters such as the performance of the pumps.

After the pressure constraints and other abnormal events are removed, the plasma pump flow rate  $Q_P$  is restored from the rest state and the procedure for the restoration is essentially the same as the already-described procedure for starting the operation of the plasma pump.

The start of the replacement fluid pump is in principle regulated by TMP2 (=  $P_4 - P_5$ ) which represents the pressure difference across the separation membrane in the plasma fractionator, and the replacement fluid pump flow rate  $Q_R$  is not only controlled by the replacement fluid flow setting device but also restricted by the plasma pump flow rate  $Q_P$ .

The replacement fluid pump is so set that it will stop when TMP2 is below the threshold pressure setting  $P_{\alpha}$  (TMP2 <  $P_{\alpha}$ ) whereas it starts to run if TMP2 is equal to or greater than  $P_{\alpha}$  (TMP2  $\geq$   $P_{\alpha}$ ). The value of  $P_{\alpha}$  is set at the smallest pressure difference (e.g. 50 mmHg) that is believed to achieve the required separation between the high- and low-molecular weight components of plasma by the separation membrane.

If TMP2 exceeds a limiting value (e.g. 300 mmHg), the situation is regarded as reflecting the extensive plugging of the separation membrane, so that the step of plasma fractionation is stopped and the process goes to the step of back-flushing the separation membrane, which is described below.

Thus, the replacement fluid pump will execute the operation for discharging the high-molecular weight component of plasma and the supply of the replenishing fluid only when TMP2 is within the range of 50 to 300 mmHg.

In another embodiment of the invention, the replacement fluid pump may be actuated without reference to the setting of  $P_{\alpha}$ . In this case, the operation of the replacement fluid pump is controlled on the basis of the plasma pump flow rate  $Q_P$ .

In the usual situation, the replacement fluid pump flow rate  $Q_R$  is controlled to be equal to the target replacement fluid flow rate  $Q_{Rs}$  (2.0 to 40 mL/min) which is set by the replacement fluid flow setting device. Specifically, immediately after the start of its operation, the replacement fluid pump flow rate is increased toward  $Q_{Rs}$  at the preset acceleration  $V_{r1}$ .

It should, however, be noted that the replacement fluid pump flow rate  $Q_R$  is so set that it will not exceed the prescribed flow  $Q_{Ra}$  which is calculated on the basis of the plasma pump flow rate  $Q_P$  to be equal to  $cQ_P$  ( $0 < c < 1$  and, in the usual case,  $c$  is set to be about 0.5). In other words,  $Q_R < cQ_P$  is the condition that must preferentially be satisfied by the replacement fluid pump. Therefore, if pressure constraints or any other abnormal events make it necessary to reduce the plasma pump flow rate  $Q_P$ , thereby creating the relation  $cQ_P \leq Q_{Rs}$ , the replacement fluid pump flow rate  $Q_R$  is reduced until it becomes equal to  $cQ_P$ .

When the abnormal event is removed and the plasma pump flow rate  $Q_P$  is restored, causing the prescribed flow  $Q_{Ra}$  to exceed the target replacement fluid flow rate  $Q_{Rs}$ , the replacement fluid pump flow rate  $Q_R$  is increased toward

QRs at the acceleration  $Vr_1$ .

The replacement fluid pump flow rate QR may sometimes be set within an extremely small range (e.g. 2 to 10 mL/min) as in the case where the target replacement fluid flow rate QRs is set at a very small value by means of the replacement fluid flow rate setting device or in the case where the prescribed flow rate QRa becomes very small due to the decrease in the plasma pump flow rate. In these cases, the replacement fluid pump is operated intermittently in order to assure the precision of pump operation thereby stabilizing the replacement fluid flow rate. The flow rate during the intermittent operation of the replacement fluid pump may be defined in terms of a mean flow per minute.

By the intermittent operation of the replacement fluid pump, not only is the replacement fluid flow stabilized but also the channel for discharging the high-molecular weight component of plasma is continually opened and closed; hence, TMP2 can be maintained at a comparatively high value even if only a small amount of plasma is supplied to the plasma fractionator. As a result, the low-molecular weight component of plasma can be separated from the high-molecular component efficiently to prevent the loss of plasma. (Plasma recovery step)

After the required plasma treating steps end, the residual plasma in the plasma fractionator must be recovered and returned to the patient. To meet this need, the apparatus of plasma treatment of the example under discussion is adapted to be such that the plasma fractionator can be supplied with physiological saline by means of the replacement fluid pump from the physiological saline supply means connected to the replenishing fluid supply channel.

For plasma recovery, the associated valves are switched to form the necessary fluid channel as shown in Fig. 8 and physiological saline is introduced into the plasma fractionator by means of the replacement fluid pump so that the low-molecular weight component of plasma which remains outside the separation membrane in the plasma fractionator is forced into the plasma circuit and thence returned to the patient through the return circuit. In this case, the upper limit of QRs - 1 which represents the target flow rate to be recovered through replacement by means of the replacement fluid pump is 70 mL/min and, in addition, P5 representative of the pressure outside of the separation membrane is controlled not to exceed the upper limit of the venous blood pressure P7, which is set about 20 mmHg lower than the threshold for the issuance of an alarm signal.

(Backflushing step)

During the plasma treatment, the separation membrane in the plasma fractionator may be plugged to introduce difficulty in continuing the normal plasma treatment. This situation is recognized by the increase of TMP2 (typically above 300 mmHg) and can be dealt with by backflushing the separation membrane, in which physiological saline is supplied on the secondary side of the plasma fractionator and allowed to flow from the outside to the inside of the separation membrane.

To perform the backflushing step, the necessary flow channel is formed as shown in Fig. 9 and the replacement fluid pump is operated to supply physiological saline from its supply means to the secondary side of the plasma fractionator while discharging the fluid on the primary side of the separation membrane. In this case, the upper limit of QRs - 2 which represents the target flow rate of backflushing through replacement by means of the replacement fluid pump is 100 mL/min and, in addition, the pressure outside of the separation membrane being monitored by pressure sensor P5 is controlled not to exceed the upper limit, which is set about 20 mmHg lower than the threshold for the issuance of an alarm signal.

According to the embodiment of the present invention, plasma is processed in such a way that when the pressures being monitored by specified pressure gauges deviate from the respective limiting values to cause pressure constraints, various pump flow rates are reduced rapidly enough to ensure that the pressure constraints can be removed as soon as possible. After the pressure constraints are removed, the pump flow rates are restored to preset accelerations, again ensuring that there will be no excessive pressure buildups due to abruptly increasing loads.

If the blood pump flow rate is increased through two stages of acceleration when a blood sample is introduced immediately after the apparatus is started to operate, there will be no possibility of imposing an abrupt load on the apparatus and the target blood flow rate can be rapidly reached without causing a pressure buildup exceeding the limiting value. This is also true with the plasma pump and if its flow rate is increased through two stages of acceleration, the desired target plasma flow rate can be rapidly reached without causing a departure from the limiting value of pressure.

If any abnormal event other than pressure constraints occurs while the blood pump is operating normally, the blood pump is controlled in such a way that its flow rate is decelerated rapidly while a standby flow rate is maintained at a value not exceeding a preset upper limit; this ensures safety in the blood treatment without stopping its flow, thereby preventing the blood from being coagulated in the circuits.

If the plasma pump flow rate is controlled as a function of the pressure difference across the separation membrane in the plasma separator, it can be set at an optimal value reflecting the degree of plugging of the separation membrane which is variable at every moment. As a result, the progress of the plugging of the separation membrane can be retarded and the required plasma treatment can be accomplished without being interrupted or undergoing some constraints.

If the condition for actuating the replacement fluid pump is specified in terms of the pressure difference across the separation membrane in the plasma fractionator, with the upper limit of the replacement fluid pump flow rate being determined on the basis of the plasma pump flow rate, the high-molecular weight component of plasma can be discharged only when the low-molecular weight component is being separated efficiently; as a result, the loss of plasma can be prevented.

If the replacement fluid pump is run intermittently, the precision of its operation in the range of extremely small flow rates is effectively maintained to permit for the stabilization of the flow rate. Hence, even if the replacement fluid pump is operated at a very small flow rate, the pressure difference across the separation membrane in the plasma fractionator can be maintained at a comparatively high level to ensure that the low-molecular weight component of plasma can be separated with high efficiency; as a result, the loss of plasma is prevented.

Fig. 10 shows an apparatus for treating blood by plasma exchange and comprises basically a collection circuit for withdrawing a blood sample and feeding it into a plasma separator by means of a blood pump, a reject plasma channel for separating plasma from the blood in the plasma separator and discharging the separated plasma by means of a plasma exchange pump, means of supplying a replenishing fluid, a replenishing fluid supply channel for communicating the replenishing fluid supply means with a return circuit via the plasma exchange pump, and the return circuit for returning the blood permeate from the plasma separator after it is combined with the replenishing fluid.

In the embodiment to be described below, a plasma exchange pump of a twin type is employed. This provides for simultaneous fitting of two tubes, one serving as the reject plasma channel and the other serving as the replenishing fluid supply channel. As a result, the passage of plasma through the reject plasma channel and that of the replenishing fluid through the replenishing fluid supply channel can be accomplished simultaneously with a single pump unit, thereby assuring the plasma to be exchanged with an equal volume of the replenishing fluid.

Provided at appropriate sites in the circuits are a pressure gauge P3, drip chambers D1, D2, D6 and D7 fitted with pressure gauges P1, P2, P6 and P7, as well as clamp valves V1, V9, V12, V13, V14 and V15 for performing ON/OFF and switching control over the flow channels. Also provided are infusers of physiological saline for rinsing the circuits and recovering the residual blood, an infuser of anticoagulant heparin, a blood leak detector for detecting the leakage of blood into the plasma emerging from the plasma separator, a blood warmer for warming the returning blood to a specified temperature, an air bubble detector for detecting the entrance of air bubbles into the returning blood, fluid shortage detectors for checking the supply of physiological saline and the replenishing fluid, and any other necessary devices.

The procedure of blood processing steps will now be outlined. Usually, the execution of blood treatment is preceded by the preparative steps of setting up the respective circuits and rinsing their interior with physiological saline. When the required preparation steps end, the blood pump is started to run so that a blood sample is withdrawn into the collection circuit through the collection tip and thence supplied into the plasma separator. The plasma separated from the blood in the plasma separator is forced by means of the plasma exchange pump to be discharged through the reject plasma channel. At the same time, the driving force provided by the plasma exchange pump allows the replenishing fluid to be introduced into the replenishing supply channel from the replenishing fluid supply means in a volume equal to that of the discharged plasma. The introduced replenishing fluid is supplied into the return circuit and returned to the patient after being combined with the blood permeate from the plasma separator.

The value of QP which represents the target plasma flow rate for the plasma exchange pump is given as a function of the blood pump flow rate QB and the pressure difference across the separation membrane TMP. In other words, the plasma exchange pump is controlled to provide the target plasma flow rate QP which is calculated at every moment based on the actual blood pump flow rate QB and the ratio determined from TMP.

In order to ensure that an abrupt load is not exerted on the separation membrane in the plasma separator to cause an excessive pressure buildup, the initial acceleration  $V_{p0}$  for the plasma exchange pump is usually set at a lower value than the normal acceleration  $V_{p1}$ . However, this is not always the case and depending on the specific situation of the treatment,  $V_{p0}$  may be set to be greater than  $V_{p1}$ .

If the value of pressure TMP being monitored with the associated pressure sensor deviates from the limiting value to cause a pressure constraint, the plasma exchange pump flow rate QP is reduced at a specified deceleration  $V_{p2}$ , which is set at a sufficiently great value to ensure that the pressure constraint can be removed rapidly. If the pressure constraint is removed, the plasma exchange pump flow rate QP is increased at the normal acceleration  $V_{p1}$  such that it is reverted toward the target plasma flow rate QPs.

Thus, in the present invention, if a pressure constraint is exerted on either pump whether it is the blood pump or the plasma exchange pump, the pump flow rate is reduced at a comparatively large deceleration, thereby allowing for rapid elimination of the abnormal pressure state. During the restoration phase, the pump flow rate is increased mildly enough to avoid the excessive pressure buildup due to an abruptly increasing load and this enables the pumps to be operated with reduced occurrence of constraints.

If the plasma blood pump flow rate is to be reduced due to pressure constraints while the plasma exchange pump is running normally, the exchange pump flow rate QP is reduced synchronously. In this case, the plasma exchange

pump flow rate is determined on the basis of blood pump flow rate by the same technique as employed to calculate the target plasma flow rate QPs. It should, however, be noted that if the blood pump flow rate becomes lower than the prescribed value, the plasma exchange pump is brought to a stop.

The above-described procedures of controlling the pumps are illustrated by timing charts in Fig. 11.

5 An example of the method of setting conditions for the case of executing the blood treating steps by means of the blood processor shown in Fig. 10 will now be described below.

Immediately after the start of operation of the blood pump, the blood flow rate QB is increased at the initial acceleration  $Vb_0$  which is set at an appropriate value within the range of 20 to 100 mL/min/min. when the integrated flow has reached 300 mL which is approximately equal to the sum of the capacities of the collection circuit and the plasma separator, the initial acceleration  $Vb_0$  is switched to the normal acceleration  $Vb_1$  which is set at an appropriate value within the range of 20 to 150 mL/min/min and the blood pump flow rate is increased until the target blood flow rate QBs (= 100 mL/min) is reached. The initial acceleration  $Vb_0$  is typically set to be smaller than the normal acceleration  $Vb_1$  but this is not always the case of the invention. When the blood flow rate has reached the target value QBs, the operation of the blood pump is controlled so as to maintain QBs.

15 The operation of the blood pump is controlled in such a way that the monitored values of the blood collection pressure P1, the venous blood pressure P7 and the pressure difference across the plasma separator  $\Delta P2/6$  will not exceed the limits of the respective values. If either one of said pressures deviates from the associated limiting value to cause a pressure constraint, namely, if P1 becomes lower than the lower limit, or if P7 exceeds the upper limit, or if  $\Delta P2/6$  becomes greater than the upper limit, the blood pump flow rate QB is rapidly reduced at a sufficiently great deceleration of  $Vb_2$  (= 300 mL/min/min) to ensure that the pressure constraint is removed as soon as possible. When the pressure constraint is removed, the blood pump flow rate QB is increased again at the normal acceleration  $Vb_1$  such that it is reverted toward the target blood flow rate QBs (= 100 mL/min).

20 If there occurs any abnormality (as in valves) which is other than the pressure constraints while the blood pump is running normally, the blood pump flow rate QB is rapidly decelerated to the standby flow rate QBa ( $\leq 50$  mL/min) which is preset by a blood flow rate setting device and the blood circulation is continued by controlling the blood pump such as to maintain QBa. If the abnormal event under consideration is removed, QB is restored to the target value QBs. The procedure of executing the restoration to QBs has already been described above.

Referring now to the plasma exchange pump, it remains at rest until after the blood pump has run to attain a QB value of 15 mL/min. When QB has reached 15 mL/min, the plasma exchange pump is started to run. Until after the integrated plasma flow has reached 50 mL which is approximately equal to the volume of plasma on the secondary side of the plasma separator, the plasma pump flow rate QP is increased at an initial acceleration of  $Vp_0$  which is set within the range of 10 to 60 mL/min/min. Once the integral plasma flow has reached 50 mL, the plasma pump flow rate QP is increased at a normal acceleration  $Vp_1$  (10 to 100 mL/min/min) until it reaches the target plasma flow rate QPs. In order to ensure that the load on the machine parts will increase mildly, the normal acceleration  $Vp_1$  is usually set to be greater than the initial acceleration  $Vp_0$ .

35 The plasma pump is controlled at every moment such as to maintain the target plasma flow rate QPs which is calculated on the basis of QB and TMP.

The target plasma flow rate QPs is expressed as  $QPs = K \cdot R1 \cdot QB$ , where QB is the blood pump flow rate, K is a coefficient of plasma flow ratio which is preset by a plasma flow ratio setting device and R1 is a coefficient defined below on the basis of TMP:

$$R1 = 1.0 - (TMP/\text{upper limit of TMP}) \cdot (1.0 - r)$$

45 where r is a coefficient of the upper limit of pressure difference and set at an appropriate value between 0.0 (inclusive) and 1.00 depending on the degree of internal plugging of the separation membrane. Depending on the properties of the blood to be treated and the quality of the separation membrane, the separation membrane occasionally has a great tendency to be plugged. If it is empirically known that the separation membrane is likely to be plugged, the value of r is set in the lower range. On the other hand, if it is empirically known that the separation membrane is free from the potential plugging, the value of r may be set in the higher range.

50 The coefficient of plasma flow ratio K is a parameter which is set by the plasma flow ratio setting device in consideration of the performance of the plasma separator and the properties of the blood to be treated and it is generally set within the range of 0.2 to 0.4, typically within the range of 0.25 to 0.35.

If TMP deviates from the limiting value, the plasma exchange pump flow rate QP is rapidly reduced at the specified deceleration  $Vp_2$  (e.g., 140 mL/min/min). If the pressure constraint is eventually removed, QP is increased again at the normal acceleration  $Vp_1$  so that it is reverted toward the target plasma flow rate QPs.

55 It should be noted that the limiting values of the various pressures to be monitored, namely, the lower limit of blood correction pressure P1, the upper limit of venous blood pressure P7, the upper limit of the pressure difference across the plasma separator  $\Delta P2/6$  and the upper limit of the pressure difference across the separation membrane TMP, are

each set to be a little lower than the threshold for the issuance of an alarm signal so as to assure safety in the treating operations. Specifically, a difference of about 20 mmHg is provided between the threshold and the respective limiting value.

The plasma exchange pump is not operated independently of the blood pump but the two pumps are controlled in operative association with each other. Even if the plasma exchange pump is running normally, it may become necessary to reduce the blood pump flow rate QB on account of a pressure constraint; in that case, the plasma exchange pump flow rate QP is reduced synchronously such that the relation  $QP = K \cdot R1 \cdot QB$  (for the definitions of K and R1, see above) is maintained at all times. If the blood pump flow rate QB is adjusted to be equal to the standby flow rate QBa when an abnormal event (as in valves) which is other than pressure constraints occurs, the plasma exchange pump should, in principle, be brought to a stop.

In the embodiment under consideration, the plasma exchange pump is so set that it will stop running if the blood pump flow rate QB falls below a certain value (e.g. 15 mL/min). It should, however, be noted that the lower limit of QB below which the plasma pump is brought to a stop is not necessarily 15 mL/min but may be determined as appropriate for parameters such as the performance of the pumps.

After the pressure constraints and other abnormal events are removed, the plasma exchange pump flow rate QP is restored and the procedure for the restoration is essentially the same as the already-described procedure for starting the operation of the plasma exchange pump.

According to the embodiment of the present invention, blood is processed in such a way that when the pressures being monitored by specified pressure sensors deviate from the respective limiting values to cause pressure constraints, various pump flow rates are reduced rapidly enough to ensure that the pressure constraints can be removed as soon as possible. After the pressure constraints are removed, the pump flow rates are restored at preset accelerations, again ensuring that there will be no excessive pressure buildups due to abruptly increasing loads.

If the blood pump flow rate is increased through two stages of acceleration when a blood sample is introduced immediately after the apparatus is started to operate, there will be no possibility of imposing an abrupt load on the apparatus and the target blood flow rate can be rapidly reached without causing a pressure buildup exceeding the limiting value. This is also true with the plasma exchange pump and if its flow rate is increased through two stages of acceleration, the desired target plasma flow rate can be rapidly reached without causing a departure from the limiting value of pressure.

If any abnormal event other than pressure constraints occurs while the blood pump is operating normally, the blood pump is controlled in such a way that its flow rate is decelerated rapidly while a standby flow rate is maintained at a value not exceeding a preset upper limit; this ensures safety in the blood treatment without stopping its flow, thereby preventing the blood from being coagulated in the circuits.

If the plasma pump flow rate is controlled as a function of the pressure difference across the separation membrane in the plasma separator, it can be set at an optimal value reflecting the degree of plugging of the separation membrane which is variable at every moment. As a result, the progress of the plugging of the separation membrane can be retarded and the required blood treatment can be accomplished without being interrupted or undergoing some constraints.

#### Claims

1. A method of blood treatment in such a way that a blood sample withdrawn by a blood pump provided in a collection circuit is fed into a treatment circuit, where it is subjected to specified treatment and thence returned to the patient through a return circuit, said method comprising the steps of:

starting the treatment and continuing it with a blood pump flow rate being increased at a preset normal acceleration until a specified target blood flow rate is reached;  
controlling the operation of said blood pump such as to maintain said target blood flow rate once it has been reached;  
reducing said blood pump flow rate at a specified deceleration if values of pressure as detected by specified pressure gauges provided at appropriate sites in the collection, treatment and return circuits or the values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints; and  
if said pressure constraints are removed, increasing said blood pump flow rate at said normal acceleration so that it is reverted toward said target blood flow rate.

2. A method according to claim 1, wherein since the start of blood treatment, said blood pump flow rate is increased through at least two stages of acceleration, one being at a preset initial acceleration and the other being at the normal acceleration, until said target blood flow rate is reached.

3. A method according to claim 1 or 2, wherein if any abnormal event other than said pressure constraints occurs during the operation of said blood pump, said blood pump flow rate is reduced at a specified deceleration and thereafter maintained at a standby flow rate not exceeding a preset limiting value.
- 5 4. A method according to claim 1, 2 or 3, wherein the treatment circuit includes an adsorptive blood treatment circuit in which a plasma separated from the blood sample by means of a plasma separator is directed by a plasma pump into an adsorber where unnecessary components are adsorptively removed from the plasma, and said method further comprising the steps of:
  - 10 starting said plasma pump after said blood pump rate exceeds a prescribed value;
  - increasing a plasma pump flow rate at a preset normal acceleration after the start of said plasma pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached;
  - controlling the operation of said plasma pump such as to maintain said target plasma flow rate once it has been reached;
  - 15 reducing said plasma pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure gauges or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints; and
  - if said pressure constraints are removed, increasing said plasma pump flow rate at said normal acceleration so that it is reverted toward said target plasma flow rate.
- 20 5. A method according to claim 4, wherein said target plasma flow rate is calculated based on a pressure difference across a separation membrane in the plasma separator and on said blood pump flow rate.
- 25 6. A method according to claim 4 or 5, wherein if said blood pump flow rate is reduced, said plasma pump flow rate is synchronously controlled toward said target plasma flow rate calculated based on said blood flow rate.
7. A method according to any one of claims 1 to 6, wherein said treatment circuit includes a double filtration circuit in which a plasma separated from the blood sample in a plasma separator is directed by means of plasma pump into a plasma fractionator, where it is fractionated into high-molecular weight component and low-molecular weight component, and the high-molecular weight component is discharged while a replenishing fluid is supplied to the low-molecular weight component by means of a replacement fluid pump, said method comprising the steps of:
  - 30 starting said plasma pump after said blood pump rate exceeds a prescribed value, increasing a plasma pump flow rate at a preset normal acceleration after the start of said plasma pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached, controlling the operation of said plasma pump such as to maintain said target plasma flow rate once it has been reached, reducing said plasma pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure sensors or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints, and if said pressure constraints are removed, increasing said plasma pump flow rate at said normal acceleration so that it is reverted toward said target plasma flow rate; and
  - 40 stopping said replacement fluid pump if a calculated value obtained from pressure values detected by the specified pressure gauges is below a preset value, starting said replacement fluid pump after the calculated value exceeds said present value so as to increase a replacement fluid flow rate toward a predetermined target replacement fluid flow rate at a preset acceleration, and controlling the operation of said replacement fluid pump so as to maintain a lower one of said target replacement fluid flow rate and a prescribed flow rate calculated base on said plasma pump flow rate.
- 45 8. A method according to claim 7, wherein the operation of said replacement fluid pump is controlled based on a pressure difference across a separation membrane in said plasma fractionator.
- 50 9. A method according to claim 7 or 8, wherein said replacement fluid pump is operated intermittently.
10. A method according to any one of claims 1 to 9, wherein said processing circuit includes a plasma exchange circuit in which a plasma separated from the blood sample in a plasma separator is exchanged with a replenishing fluid by means of a plasma exchange pump, and said method further comprising the steps of:
  - 55 starting said plasma exchange pump after said blood pump flow rate exceeds a prescribed value;
  - increasing a plasma exchange pump flow rate at a preset normal acceleration after the start of said plasma

exchange pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached;

controlling the operation of said plasma exchange pump such as to maintain said target plasma flow rate once it has been reached;

5 reducing said plasma exchange pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure gauges or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints; and

if said pressure constraints are removed, increasing said plasma exchange pump flow rate at said normal acceleration so that it is reverted toward said target plasma flow rate.

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11. An apparatus for blood treatment comprising a collection circuit into which a blood sample is withdrawn by means of a blood pump, a treatment circuit for performing specified treatment on the withdrawn blood sample and a return circuit through which the treated blood sample is returned to the patient, said apparatus further including means for controlling the operation of the blood pump, and pressure gauges provided at appropriate sites in the collection, treatment and return circuits, said control means being set in such a way that since the start of blood treatment, said blood pump flow rate is increased at a preset normal acceleration until a specified target blood flow rate is reached, that once said target blood flow rate has been reached, said blood pump is operated so as to maintain said target blood flow rate, that said blood pump flow rate is reduced at a specified deceleration if the values of pressure as detected by specified pressure gauges or the values calculated on said pressure values deviate from respective limiting values to cause pressure constraints and that if said pressure constraints are removed, said blood pump flow rate is increased at said normal acceleration so that it is reverted to said target blood flow rate.

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12. An apparatus according to claim 11, wherein the processing circuit includes an adsorptive blood treatment circuit in which a plasma separated from the blood sample by means of a plasma separator is directed by a plasma pump into an adsorber where unnecessary components are adsorptively removed from the plasma, and said apparatus further including means for controlling the operation of said plasma pump so as to start said plasma pump after said blood pump rate exceeds a prescribed value, increase a plasma pump flow rate at a preset normal acceleration after the start of said plasma pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached, control the operation of said plasma pump such as to maintain said target plasma flow rate once it has been reached, reduce said plasma pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure gauges or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints, and increase said plasma pump flow rate at said normal acceleration so that it is reverted toward said target plasma flow rate if said pressure constraints are removed.

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13. An apparatus according to claim 11 or 12, wherein said treatment circuit includes a double filtration circuit in which a plasma separated from the blood sample in a plasma separator is directed by means of plasma pump into a plasma fractionator, where it is fractionated into high-molecular weight component and low-molecular weight component, and the high-molecular weight component is discharged while a replenishing fluid is supplied to the low-molecular weight component by means of a replacement fluid pump, said apparatus further including:

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means for controlling the operation of plasma pump so as to start said plasma pump after said blood pump rate exceeds a prescribed value, increase a plasma pump flow rate at a preset normal acceleration after the start of said plasma pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached, control the operation of said plasma pump such as to maintain said target plasma flow rate once it has been reached, reduce said plasma pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure gauges or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints, and increase said plasma pump flow rate at said normal acceleration so that it is reverted toward said target plasma flow rate if said pressure constraints are removed; and

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means for controlling the operation of said replacement fluid pump so as to stop said replacement fluid pump if a calculated value obtained from pressure values detected by the specified pressure gauges is below a preset value, start said replacement fluid pump after the calculated value exceeds said present value so as to increase a replacement fluid flow rate toward a predetermined target replacement fluid flow rate at a preset acceleration, and control the operation of said replacement fluid pump so as to maintain a lower one of said target replacement fluid flow rate and a prescribed flow rate calculated base on said plasma pump flow rate.

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14. An apparatus according to claim 11, 12 or 13, wherein said treatment circuit includes a plasma exchange circuit in which a plasma separated from the blood sample in a plasma separator is exchanged with a replenishing fluid by

means of a plasma exchange pump, and said apparatus further including means for controlling the operation of the plasma exchange pump so as to start said plasma exchange pump after said blood pump flow rate exceeds a prescribed value, increase a plasma exchange pump flow rate at a preset normal acceleration after the start of said plasma exchange pump and until a specified target plasma flow rate calculated based on the blood pump flow rate is reached, control the operation of said plasma exchange pump such as to maintain said target plasma flow rate  
5 once it has been reached, reducing said plasma exchange pump flow rate at a specified deceleration if values of pressure as detected by the specified pressure gauges or values calculated on the basis of said pressure values deviate from respective limiting values to cause pressure constraints, and increase said plasma exchange pump at said normal acceleration so that it is reverted toward said target plasma flow rate if said pressure constraints are  
10 removed.

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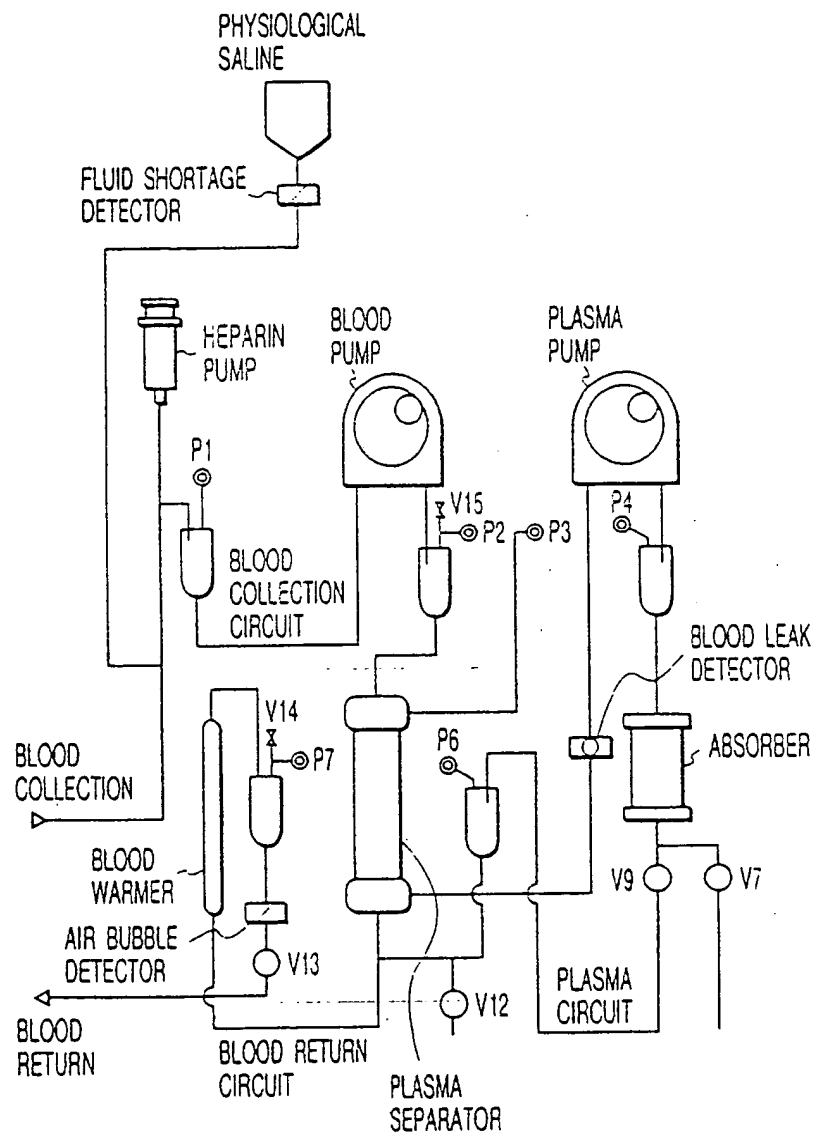
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FIG. 1



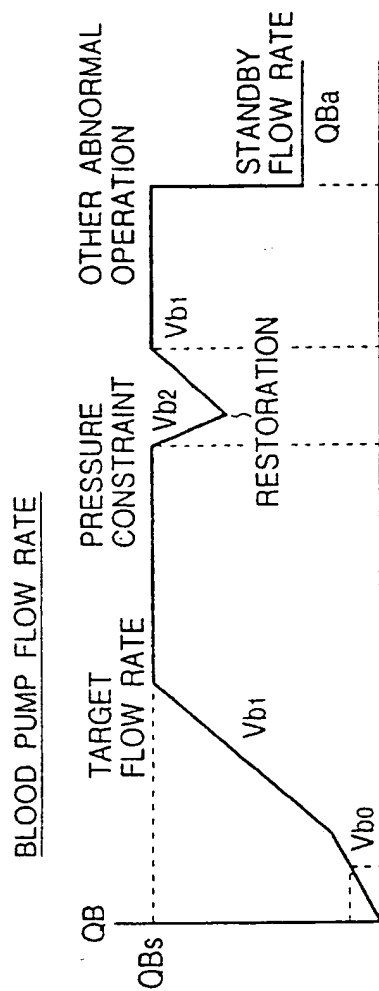


FIG. 2A

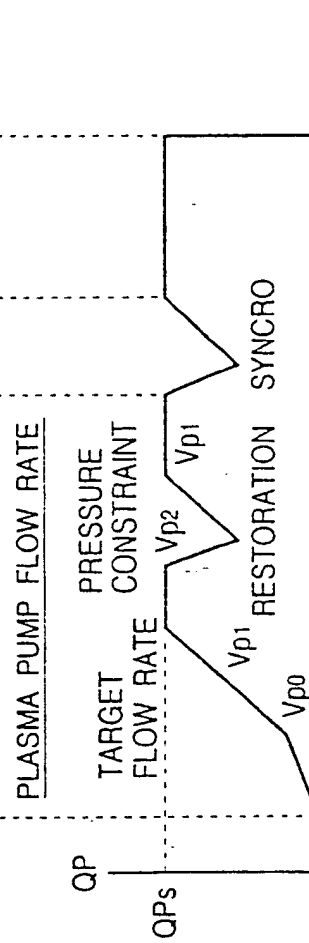


FIG. 2B

FIG. 3

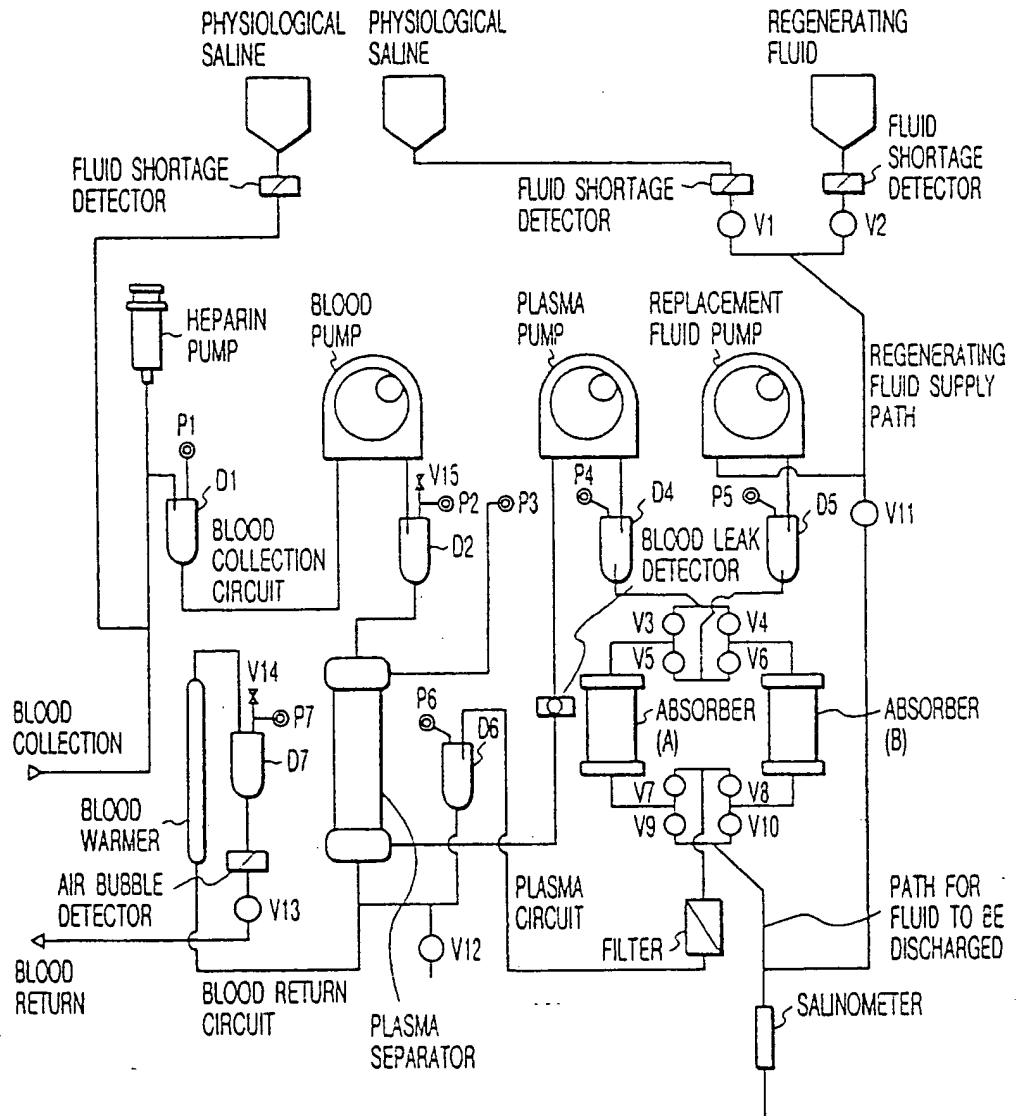


FIG. 4

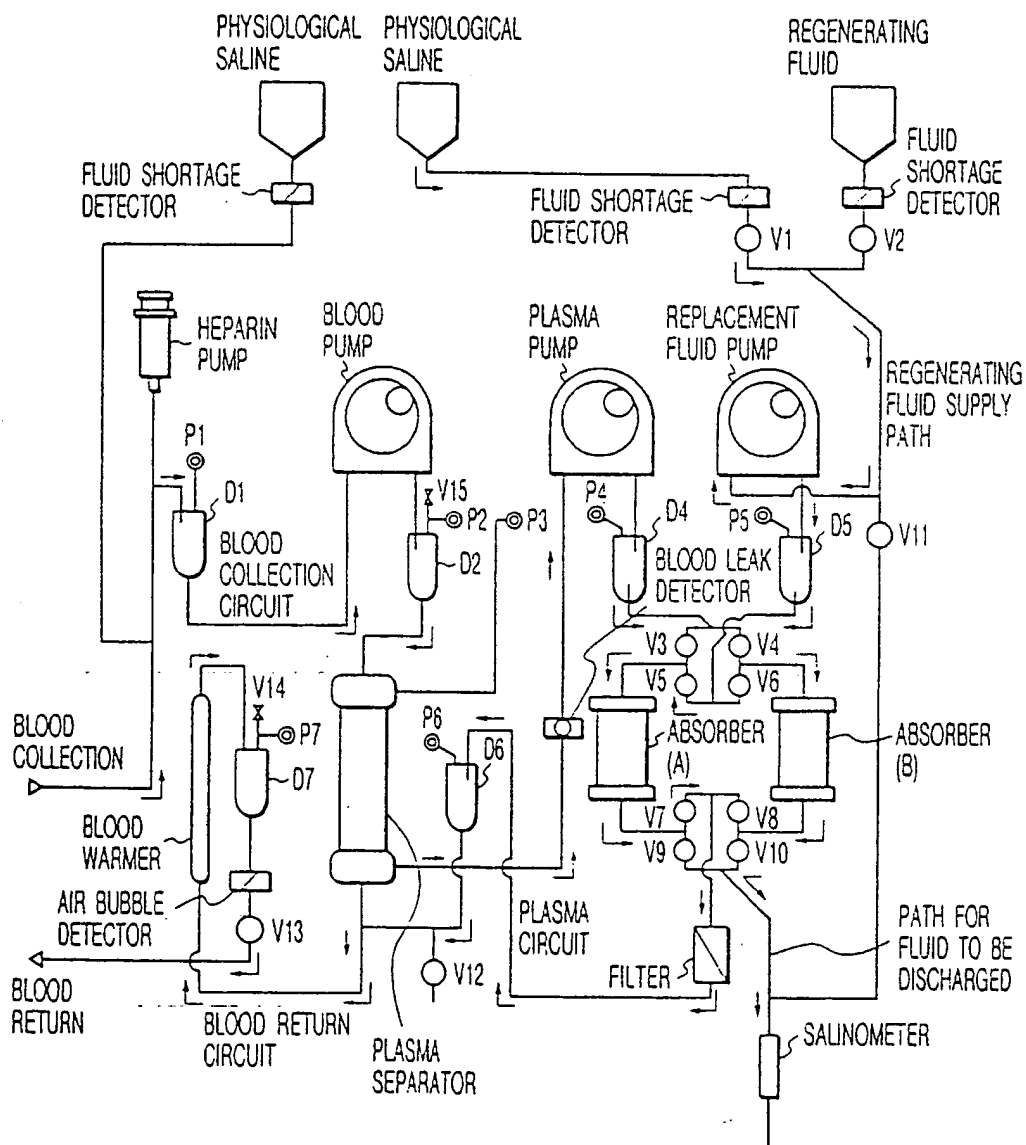


FIG. 5

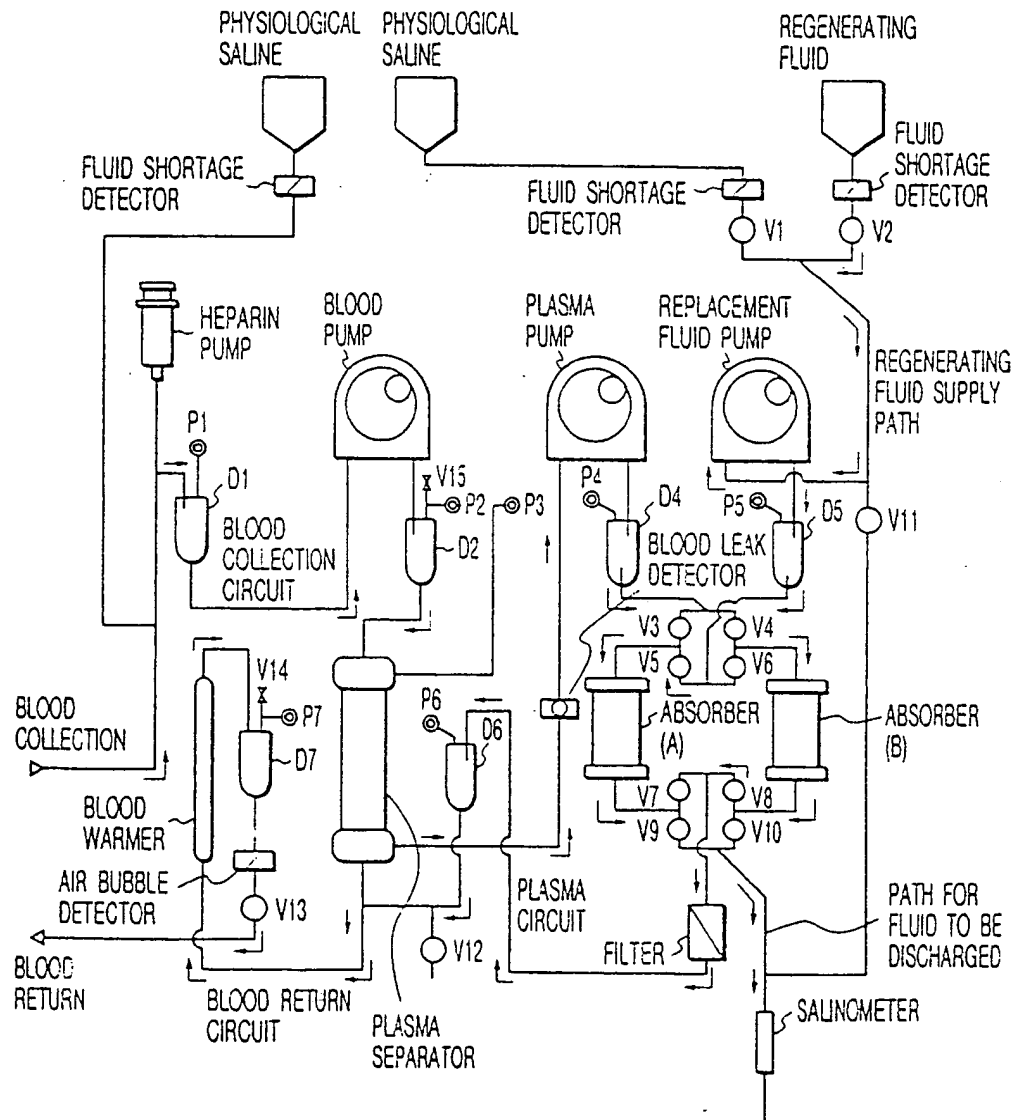
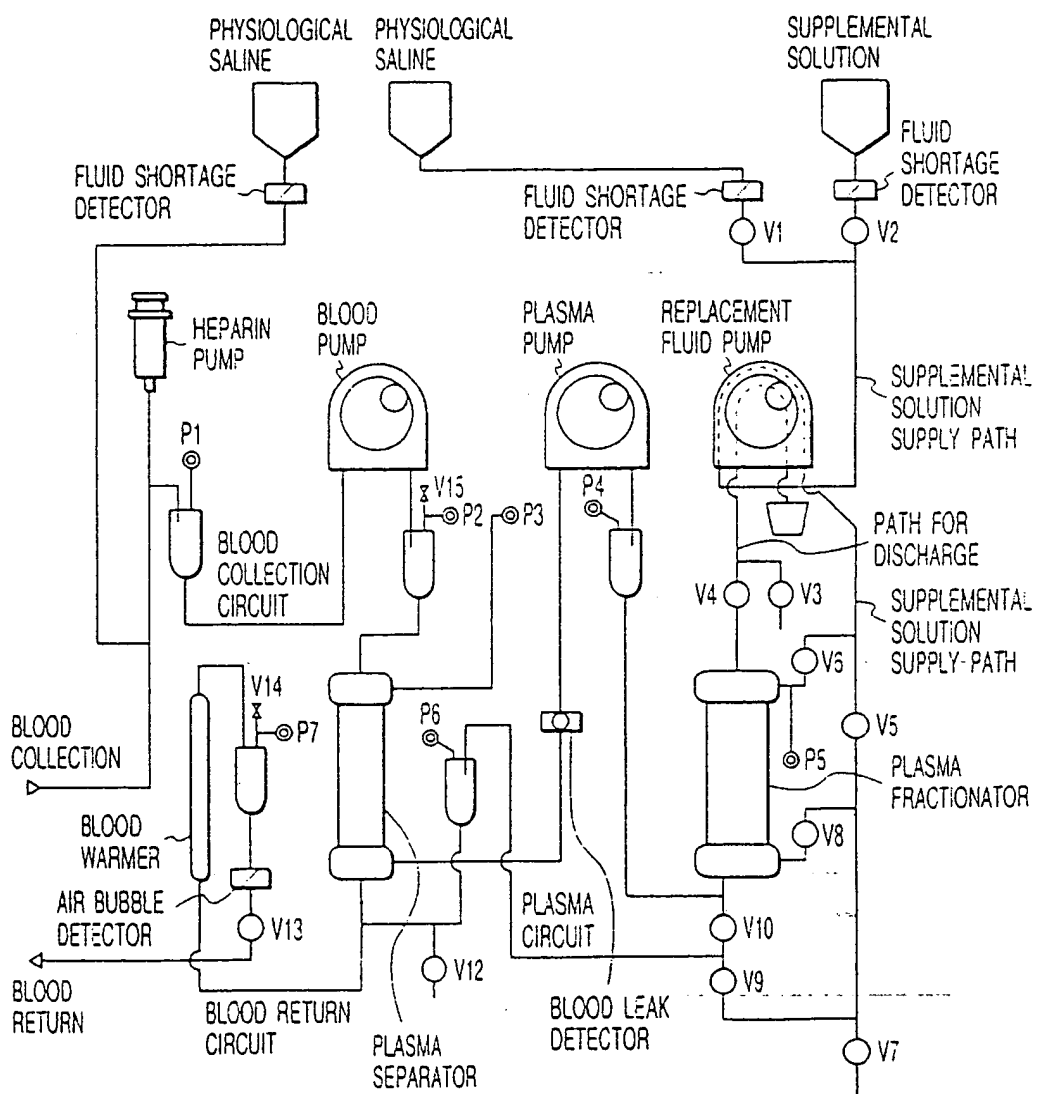


FIG. 6



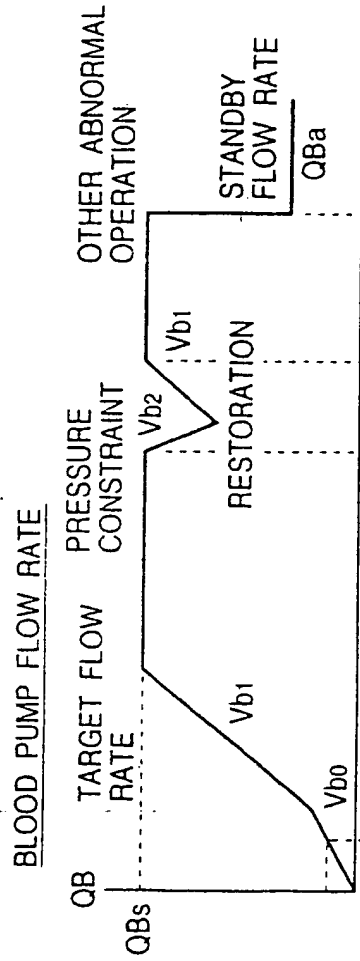


FIG. 7A

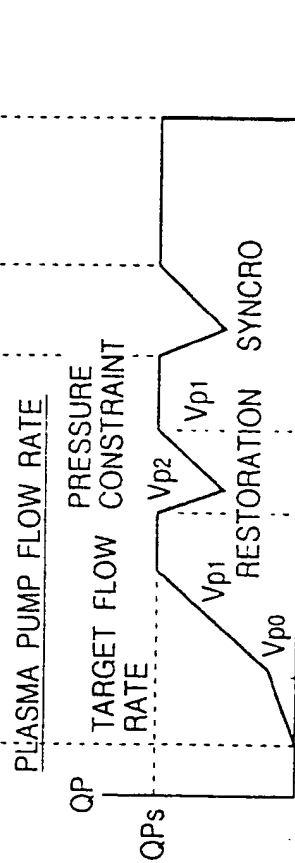


FIG. 7B

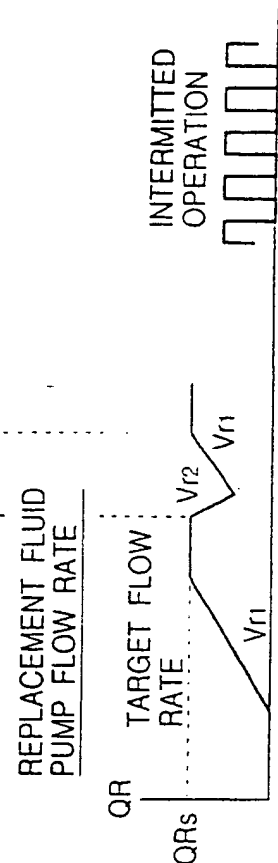


FIG. 7C

FIG. 8

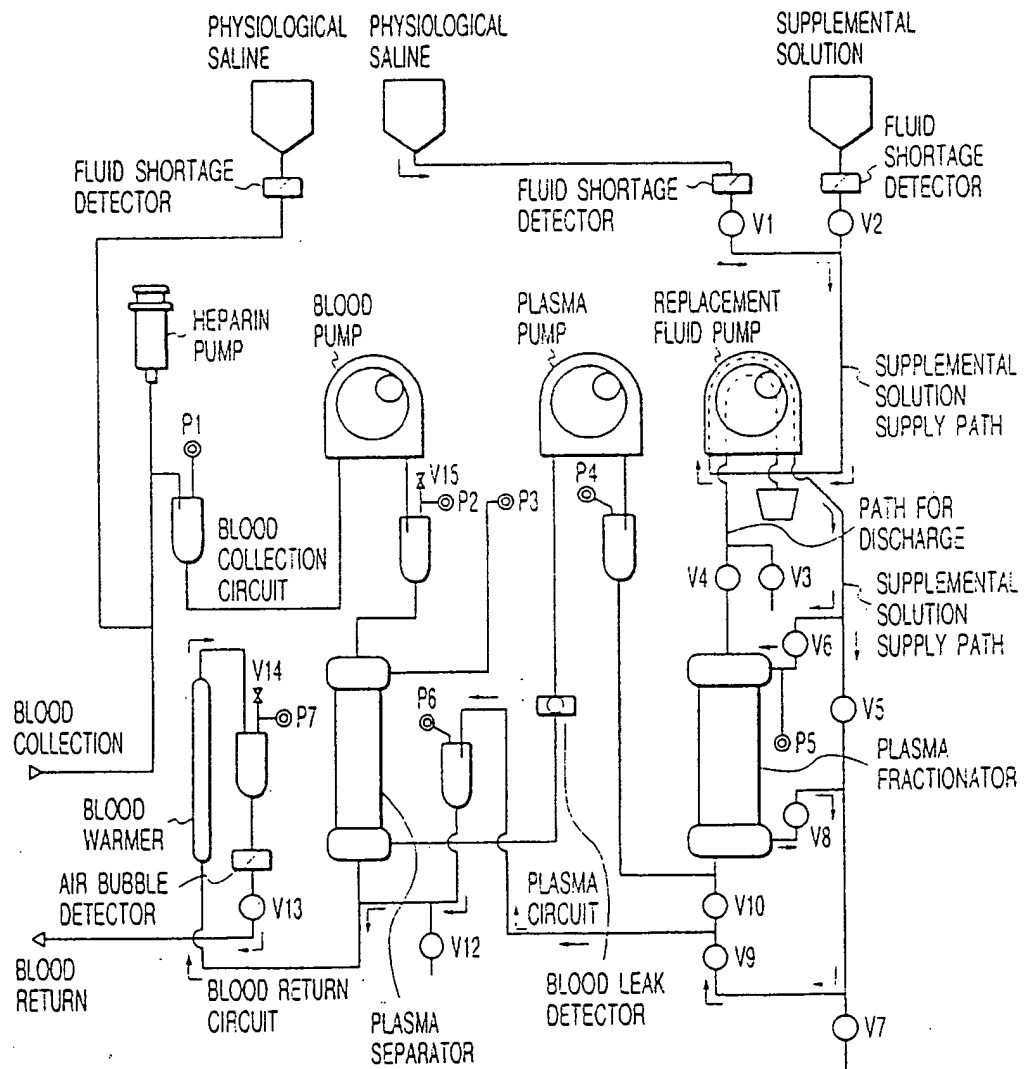


FIG. 9

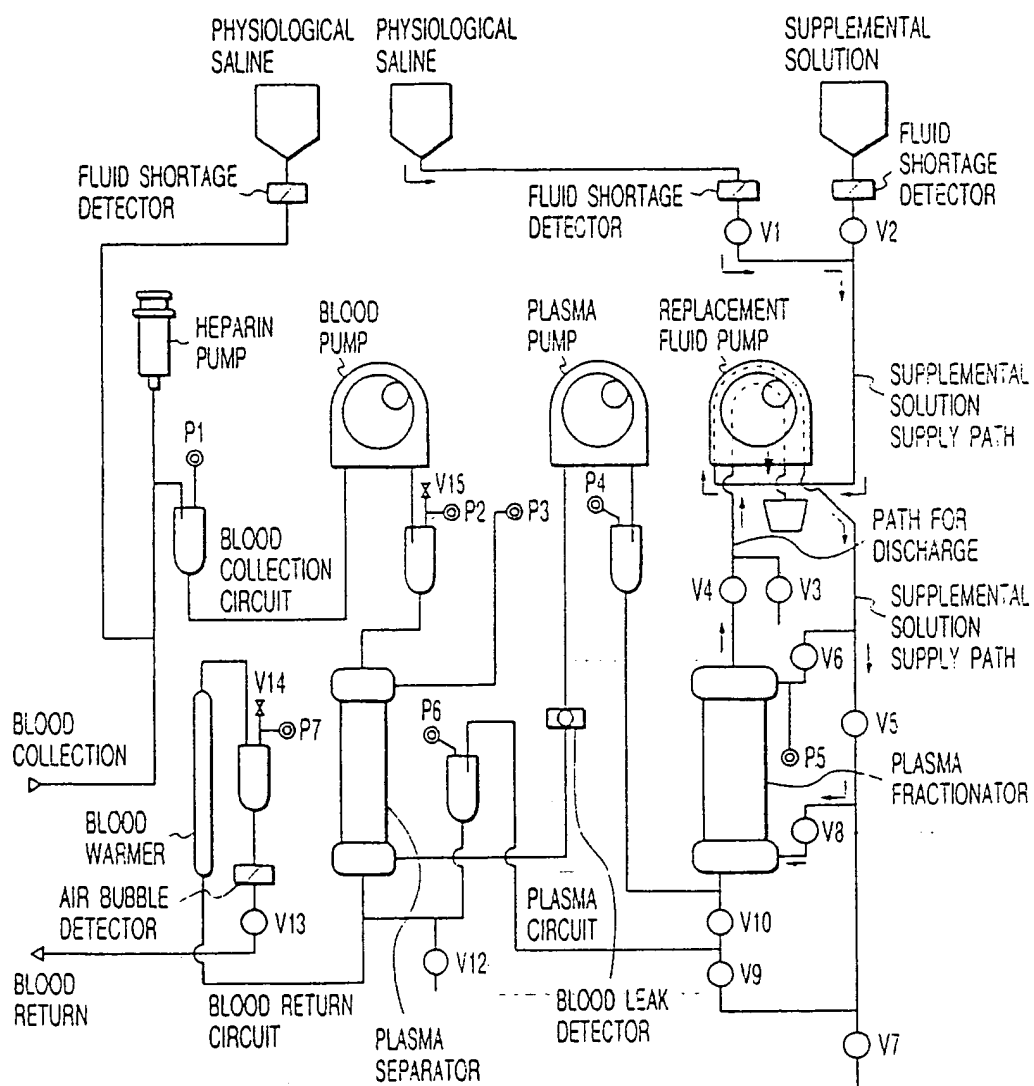
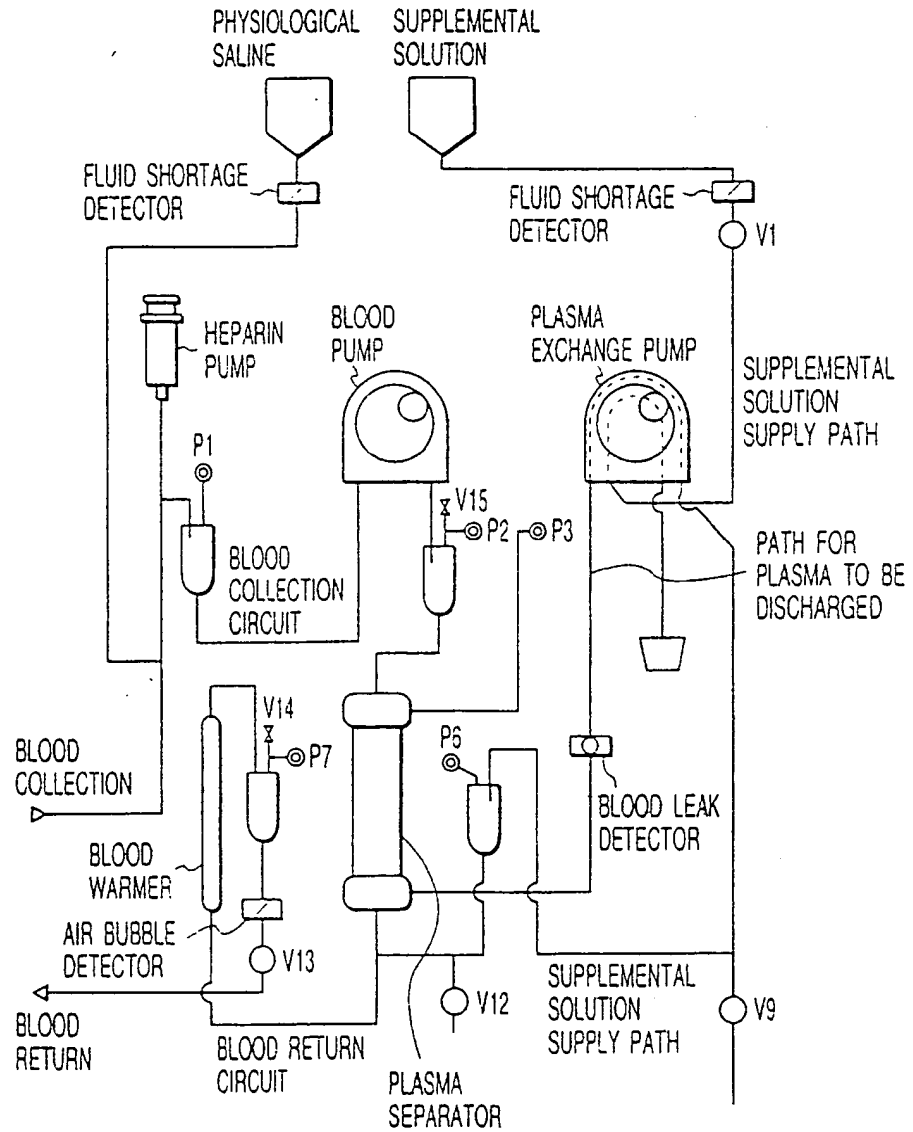


FIG. 10



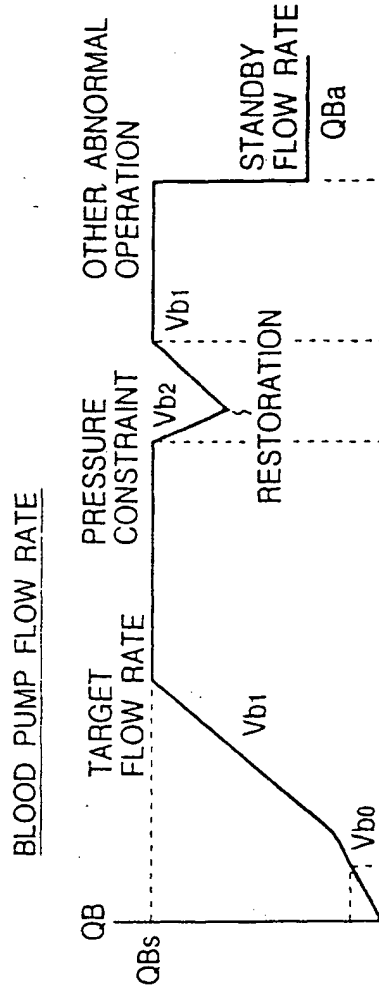


FIG. 11A

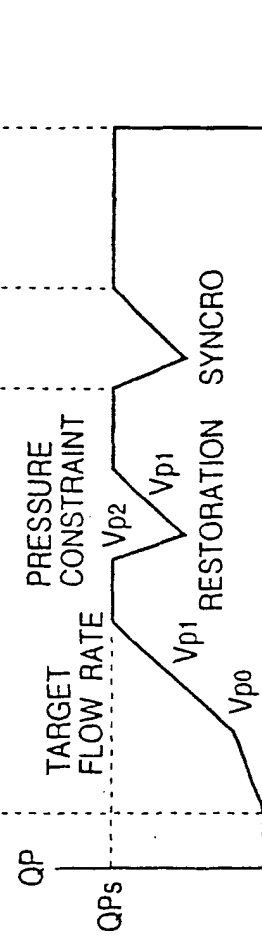


FIG. 11B



European Patent  
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# PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 97 11 5528

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 92 02264 A (BAXTER INTERNATIONAL INC.) * page 17, line 1 - line 14 * * page 31, line 32 - page 32, line 15 * * page 37, line 17 - line 27 * * page 39, line 9 - line 20 * * page 41, line 1 - line 32 * * page 42, line 36 - page 44, line 10 * * claims 1,5-11 * -----	11	A61M1/36
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61M
<b>INCOMPLETE SEARCH</b> The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims. Claims searched completely 11-14 Claims searched incompletely  Claims not searched 1 -10 Reason for the limitation of the search Article 52 (4) EPC - Method for treatment of the human or animal body by therapy			
Place of search		Date of completion of the search	Examiner
THE HAGUE		15 December 1997	Vereecke, A
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document  T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons S : member of the same patent family, corresponding document			

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